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WO 2004/099288 A1

(54) **Title:** POLYETHYLENEIMINE POLYMERS

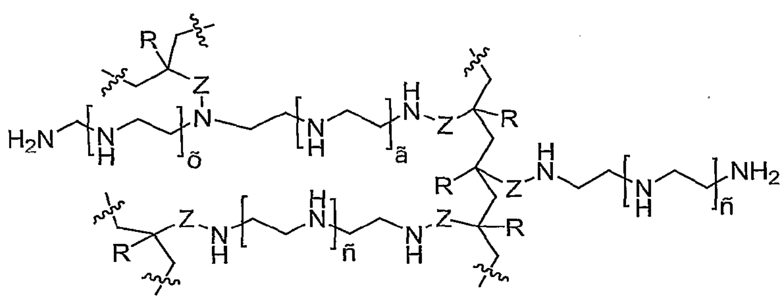
(57) **Abstract:** The present invention relates to the development of a beaded high loading capacity polymer for solid phase synthesis and purification of solution-phase organic synthesis. The matrix comprises cross-linked polyethyleneimine units as in the formula (I), where ñ is a real number of 5-1500, and designates the average degree of polymerisation (dp) of polyethyleneimine, ã and õ are real numbers ranging from O to ñ. The high density primary and secondary amino functional groups on the resin function as the site for the excess reagents to react. In a particular aspect there is provided a cross-linked polymer matrix selected from the group consisting of a cross-linked polymer matrix formed from a macromonomer comprising a polyethyleneimine functionalized with at least one fragment comprising a vinyl group, wherein said fragment can be polymerized using radical or ionic initiators to form the cross-linked polymer matrix, or a cross-linked and beaded polymer matrix formed from a macromonomer comprising a polyethyleneimine and a polyfunctional alkyllating agent, under inverse suspension or inverse emulsion polymerisation conditions.

Polyethyleneimine polymers

All patent and non-patent references cited in the present patent application is hereby incorporated in their entirety. This application is a non-provisional of U.S. provisional application Serial No. 60/468,991 filed 9 May 2003, which is hereby incorporated by reference in its entirety.

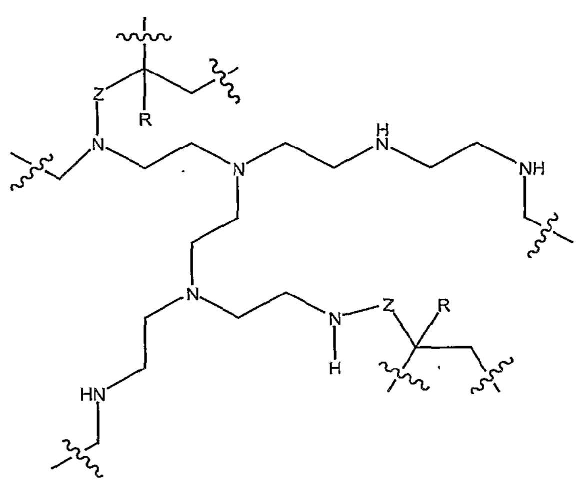
Field of invention

The present invention relates to the development of a beaded and cross-linked polymer matrix for solid phase synthesis and purification of solution-phase organic synthesis. The cross-linked polyethyleneimine units can be illustrated by formula I,



Z= CO or $COCH_2$ or SO_2 or CS or CNH or Aryl
R= H or CH_3 or C_2H_5

wherein ñ is a real number of 5-1500, and designates the average degree of polymerisation (dp) of polyethyleneimine, ã and õ are real numbers ranging from 0 to ñ, or by formula II



wherein Z is CO or $COCH_2$ or SO_2 or CS or CNH or Aryl,
wherein R is H or CH_3 or C_2H_5, and

wherein the number of ethyleneimine units is from 5 to 60000, such as from 10 to 120, for example from 121 to 1200, such as from 1201 to 23000, for example from 23001 to 50000.

The high density primary and/or secondary amino functional groups on the polymer matrix can react e.g. with excess acylating agents in solution phase reactions.

There is also provided methods for synthesising said polymer matrices as well as uses thereof in the scavenging of e.g. metal ions and excess acylating agents.

Background of invention

The investigation and exploitation of combinatorial chemistry technology has rapidly evolved during several decades. The initial revelations of its use focused on the solid-phase synthesis of oligomers of amino acids or nucleotides, or on unnatural oligomers of other chemical building blocks like peptoids [Geysen et al., J. Bioorg. Med. Chem. Lett., 3, 397 (1993); Egholm et al., J. Am. Chem. Soc., 114, 1895 (1992); Simon et al., Proc. Natl. Acad. Sci. USA, 89, 9367 (1992)].

Recently, the library synthesis of nonoligomeric small molecules has become an area of intense research activity [Wang et al., J. Med. Chem., 38, 2995 (1995)]. In any approach to produce chemical library, whether it is solid-phase or solution-phase, is the need of rapid purification, isolation, and manipulation of chemical library members during their intermediate and final synthetic steps of preparation. The solid-phase technology offers advantages like ease of separating the products from the reaction medium and the manipulation of the beads using volumetric techniques. The limitation of solid-phase technology includes the reaction scale restriction and the need of product validation, and the decrease of reactivity inherent to solid phase synthesis.

Solution-phase synthetic technology has the advantage of nonlimiting scale and can be easily manipulated. The major limitation of solution-phase synthesis is the isolation or purification of the reaction products from the reaction medium particularly when working with compound mixtures.

The use of polymeric scavenging reagents can overcome this limitation to a great extent [Booth et al., J. Am. Chem. Soc., 119, 4882 (1997)]. The theory behind this concept is that the scavenger resins containing active groups that can mimic the limiting reagent in the reaction. After the completion of the reaction, the resin can be added to the reaction mixture to bind any unreacted reagents. Filtration of resin bound reagent will yield a relatively pure product.

WO 99/22744 describes the synthesis of a poly(ethyleneimine)-acryloyl chloride polymer and its application for reducing the oxalate levels in a patient. The described cross-linking of polyethyleneimine and acryloyl chloride is most likely formed via reversible Michael addition and amide products. There is no evidence of an amide polymerisation and the conditions do not favor radical polymerisation as there are no radical initiators added. Futhermore, the agglomerate product obtained is not a crosslinked beaded resin.

Copolymers of polyethyleneimine and aliphatic polyesters can be used for solubilization of drug and a delivery system of proteins, genes or drugs EP 1 279 682.

US 4,332,916 describes the application of polyethyleneimine crosslinked cellulose sponge as an ion exchange polymer.

The application of silica gel bound polyethyleneimine for chromatographic separation of monoclonal antibody is described in US 4,469,630.

More recently a degradable poly(β-amino esters) generated from the conjugate addition of primary and secondary amine monomers with diacrylate monomers were reported for use in gene delivery [Akinc et al., J. Am. Chem. Soc., 125, 5316 (2003)].

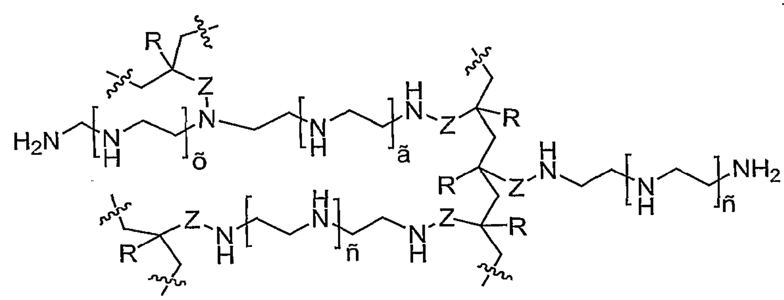
Summary of the Invention

The present invention in one aspect relates to a cross-linked polymer matrix selected from the group consisting of

i) cross-linked polymer matrices formed from a macromonomer comprising a polyethyleneimine functionalized with at least one fragment comprising a vinyl group, wherein said fragment can be polymerized using radical or ionic initiators to form the cross-linked polymer matrix, and

ii) cross-linked and beaded polymer matrices formed from a macromonomer comprising a polyethyleneimine and a polyfunctional alkylating agent, under inverse suspension or inverse emulsion polymerisation conditions.

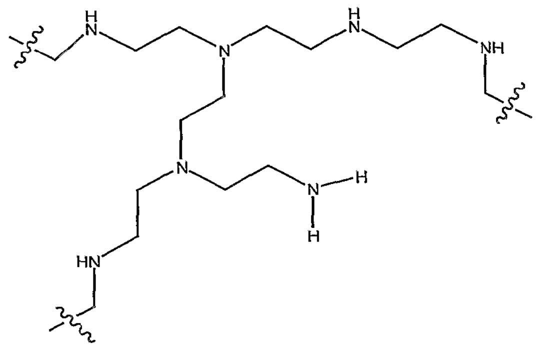
An example of a polymer matrix formed from a macromonomer comprising a polyethyleneimine functionalized with at least one fragment comprising a vinyl group capable of undergoing polymerization using radical or ionic initiators is illustrated by the formula I



Z= CO or $COCH_2$ or SO_2 or CS or CNH or Aryl
R= H or CH_3 or C_2H_5

wherein ñ is a real number of 5-1500, and designates the average degree of polymerisation (dp) of polyethyleneimine, ã and õ are real numbers ranging from 0 to ñ

An example of a cross-linked and beaded polymer matrix formed from a macromonomer comprising a polyethyleneimine and a polyfunctional alkylating agent, under inverse suspension or inverse emulsion polymerisation conditions, is illustrated by the formula V



wherein the number of ethyleneimine units is from 5 to 60000, such as from 10 to 120, for example from 121 to 1200, such as from 1201 to 23000, for example from 23001 to 50000.

One object of the present invention is the development of an efficient scavenger resin to be used e.g. in solution phase reactions for scavenging e.g. excess acylating agents with amine functional groups. It is demonstrated herein that the newly developed resins can effectively remove excess acylating agents.

The reaction of 2.5-5.0 fold excess of acylating agents, such as isocyanates, isothiocyanates, acid chlorides, alkyl chloroformates, and sulfonyl chlorides, with primary and secondary amines afforded ureas, thioureas, amides, carbamates and sulfonamides with excellent conversion and purity.

The resin can also be used for scavenging excess carbonyl compounds in addition reactions of organometallic reactants to carbonyl compounds. Also, the resin can be used as a support for solid phase organic synthesis.

The polymers resins according to the invention are short termed as ULTRAMINE.

Definitions

Beaded polymer matrix: Matrix formed by beading according to principles of suspension or inverse suspension polymerisation, by spray polymerisation, or by droplet polymerisation.

Solid phase synthesis: Synthesis where one of several of the reactants forming the target molecule is attached to a solid support e. g. a beaded polymer matrix.

Swelling: When beads or granules or particles are capable of swelling, any physical measurement of the afore-mentioned, including size determinations and volume determinations, refer to measurements conducted for the swelled bead or granule or particle. Swelling of the beads are for practical reasons measured as the volume of a packed bed of beads swollen in a specific solvent and divided by the dry weight of the beads. The unit is given as ml/g. Typical solvents are water, methanol and dichloromethane, but any suitable solvent may be chosen.

Degree of polymerisation: The number of monomeric units in a macromolecule or oligomeric molecule, a block or a chain.

Brief Description of the Drawings

Fig. 1: ULTRAMINE polymer network (formula I)

Fig 2: Synthesis of ULTRAMINE-polymer by inverse suspension polymerisation of partially derivatised polyethyleneimine

Fig. 3: Use of ULTRAMINE as a scavenger resin for the rapid purification of parallel amine acylation reactions

Fig. 4: Use of ULTRAMINE as a scavenger resin for the rapid purification of parallel addition reaction of organometallic reactants with carbonyl compounds

Fig. 5: Optical micrograph of the ULTRAMINE beads

Fig. 6: Swelling character of ULTRAMINE in various solvents

Fig. 7: Stability comparison of ULTRAMINE resin by IR spectroscopy after treatment with various reagents (a) original (b) 20% Piperidine/DMF (c) Saturated aq. NaOH (d) DBU (100%) (e) triflic anhydride (100%) (f) BF_3 Et_2O (100%) (g) BuLi (2.7 M solution in heptane, 100%) and (h) TFA (100%)

Fig. 8: Swelling character of the ULTRAMINE resin (formula I) after 7 days treatment with various reagents

Fig. 9: High performance liquid chromatogram of products (a) 1, (b) 2 (c) 7 (d) 8 (e) 9 (f) 14 (g) 15 (h) 16 (i) 21 (j) 22 (k) 23 (l) 24. Column: RCM C-18 (8 × 200 mm). Elution gradient: From 0-80% B (0.1% TFA in 10% aqueous acetonitrile) in 25 min at a flow rate of 1 ml/min. Detection 215 and 280 nm.

Fig. 10: Comparison of IR spectra (a) ULTRAMINE-Red and (b) ULTRAMINE

Detailed Description of the Invention

Polymer matrix

The polymer matrix of the present invention illustrated by formula I can be prepared by a controlled free radical polymerisation of vinyl groups in partially derivatised polyethyleneimine (Fig. 2) wherein ñ is a real number (integer) from 5 to 1500, ã and õ are real numbers ranging from 0 to 1500 and ã + õ < ñ, Z can be selected from the group consisting of CO; CO-$(CH_2)_m$; SO_2; CS; and CNH; C_6H_4; and C_6H_4-CO-$(CH_2)_m$, where $0 \leq m \leq 10$, and R can be H or CH_3 or C_2H_5.

The monomers in the Fig. 2 are a representative example and the possibility of the formation of higher substituted monomer is not excluded. The content of the macromonomers represented in the Fig. 2 is preferably at least 50% of the total mass. The beaded, insoluble cross-linked polyethyleneimines are stable in acids, bases, Lewis acids and soluble salts.

The polymer of the present invention can be used as a solid support in an array of solid phase synthetic applications, as a stationary phase in chromatography, and matrices for immobilization of macromolecules.

The polymers of the present invention can be synthesised in a wide range of molecular weights and crosslinking. The polymer can be homopolymers or copolymers and can be substituted or unsubstituted.

The polymer can be a homopolymer or a copolymer of one or more amine containing monomers in combination with one or more non-amine containing monomers. The polymer is prepared from monomers either by bulk, suspension or inverse suspension polymerisation techniques. Examples of non-amine containing monomers include vinyl alcohol such as vinyl benzyl alcohol; vinyl carboxylic acids such as acrylic acid, methacrylic acid, itaconic acid, and vinyl benzoic acid; vinyl esters such as vinyl acetate, vinyl propionate; allyl esters such as allyl acetate; allyl amines such as allyl ethyl amine; allyl alcohols such as allyl alcohol, 1-buten-3-ol, 1-penten-3-ol, 1-hexen-3-ol, 1-hydroxy-1-vinyl cyclohexane, 2-bromoallyl alcohol, 2-chloroallyl alcohol; hydroxy containing vinyl ethers such as hydroxyethyl vinyl ether; vinyl acid halides such as acryloyl chloride and methacryloyl chloride; styrenes and substituted styrenes such as 4-ethyl styrene, 4-amino styrene, dichlorostyrene, chlorostyrene, 4-hydroxystyrene, hydroxymethyl styrene, and 4-hydroxy-3-nitro styrene; vinyl toluene; hetroaromatic vinyl such as 1-vinylimidazole, 4-vinyl pyridine, and 2-vinyl pyridine; acrylamide; dimethyl acrylamide; and hydroxy containing (meth)acrylamides sucha s N-(hydroxymethyl) (meth)acrylamide, N-(1-hydroxyethyl) (meth)acrylamide, N-methyl-N-(2-hydroxyethyl) (meth)acrylamide, N-(1-hexyl-2-hydroxy-1-methylethyl) (meth)acrylamide, N-propyl-N-(2-hydroxyethyl) (meth)acrylamide. Most preferably the polymer is a homo polymer, such as a high-density amine functionality is accessible.

The polymer is insoluble by crosslinking preferably in a beaded form. The crosslinking agent can be characterised by functional groups, which react with amino group of the polyethylenimine via an amide linkage. Also a higher amino functionality and more stable polymer with polyamine network can be obtained by reducing the amide groups on the described polymer with reducing agents like borane.

The level of cross-linking makes the polymer differ in their swelling behaviour, which directly affect the reactivity of the polymer.

Methods for generating beaded polymer matrix

It is a further object of the invention to provide a method for generating a beaded polymer matrix, said method comprising the steps of

i) synthesising a monomer and/or macromonomer and a crosslinker for polymerisation, and,

ii) polymerising the polymer by either i) suspension polymerisation and/or; ii) inverse suspension polymerisation and/or iii) bulk polymerisation followed by granulation and/or iv) droplet polymerisation.

The polymerisation reaction can preferably be a radical initiated chain polymerisation reaction. The free radical initiator useful for the present invention includes azo compounds, teritiary amines, organic and inorganic peroxides and peroxodisulfates. The preferred free radical initiator is ammonuim peroxodisulfate. The commercial products include VAZO 67, VAZO 64 and VAZO 52 can also be used as the initiator.

Functional groups of the beaded polymer matrix can subsequently be reacted with different compounds as described herein elsewhere.

Applications

The beads of the invention are applicable as a scavenger resin in any type of chemical reactions involving acid chlorides, sulfonyl chlorides, isothiocyanates, cyanates, aldehydes, acids, chloroformates and anhydrides. Such chemical reaction includes, for example:

1. Synthesis of amides
2. Synthesis of ureas
3. Synthesis of carbamates
4. Synthesis of sulfonamides
5. Reactions involving excess carbonyl compounds
6. Reactions involving excess carboxylic acids
7. Reactions involving excess acid anhydrides

The polymer of the present invention can be used a solid support for a range of applications including solid phase synthesis, chromatography and immobilization of macromolecules.

The polymers according to the invention may again be derivatised with any of the commercial available linkers for solid phase synthesis. The resin can also be used for the combinatorial library synthesis.

The invention also relates to a solid support for the immobilization of proteins said support involving a polymer according to the invention as described above. Again, the invention relates to a resin for chromatographic separations such as affinity chromatography, size exclusion chromatography, ion exchange chromatography, ion pair chromatography, normal phase chromatography and reversed phase chromatography said resin involving a polymer according to the invention as described above.

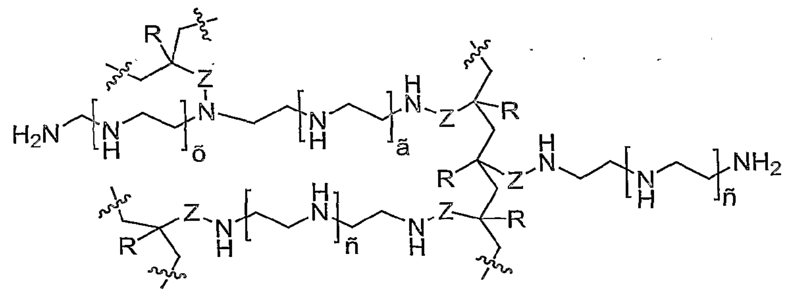
The invention also relates to a method of continuous flow or batchwise synthesis of peptides, oligonucleotides or oligosaccharides during the synthesis is attached to a solid support involving a polymer according to the invention as described above. Due to the particular features of the polymer according to the invention this method also can extend to the synthesis involving enzymatic reactions.

The invention relates to a method of immobilizing a protein wherein a protein is attached to a solid support involving a polymer according to the invention as described above.

The invention also relates to a method of performing chromatographic separations which comprises the use of a chromatographic resin involving a polymer according to the invention as described above.

In one preferred embodiment of the invention there is provided a cross-linked polymer matrix formed from a macromonomer comprising a polyethyleneimine functionalized with at least one fragment comprising a vinyl group, wherein said fragment can be polymerized using radical or ionic initiators to form the cross-linked polymer matrix.

The polyethyleneimine and the vinyl group can be linked by a unit Z preferably selected from a carbonyl group, a sulfone group, an aryl group, and derivatives thereof. The cross-linked polymer matrix preferably comprises the structure

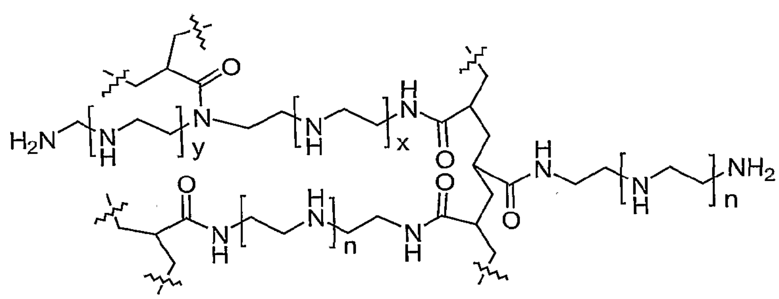


Z= CO or $COCH_2$ or SO_2 or CS or CNH or Aryl
R= H or CH_3 or C_2H_5

ñ is an integer in the range of from 5 to 1500
ã and õ are integers in the range of from 0 to ñ

In further preferred embodiments, the unit Z can be selected from the group consisting of CO; $CO\text{-}(CH_2)_m$; SO_2; CS; and CNH; C_6H_4; and $C_6H_4\text{-}CO\text{-}(CH_2)_m$, where $0 \leq m \leq 10$, such as 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10.

In another embodiment there is provided a polymer matrix comprising the structure



wherein ñ is an integer in the range of from 2 to 1550, and
wherein the sum of x and y is an integer of more than 0 and at the most ñ-1.

ñ is preferably an integer in the range of from 5 to 1500, such as from 5 to 1200, for example from 5 to 1000, such as from 5 to 800, for example from 5 to 600, such as from 5 to 400, for example from 5 to 300, for example from 5 to 200, such as from 5 to 100, for example from 5 to 90, such as from 5 to 80, for example from 5 to 70, such as from 5 to 60, for example from 5 to 50, such as from 5 to 45, for example

from 5 to 40, such as from 5 to 30, for example from 5 to 25, such as from 10 to 25, for example from 10 to 20, such as from 10 to 15, for example from 15 to 20, such as from 11 to 19, for example from 12 to 18, such as from 13 to 17, for example from 10 to 12, such as from 12 to 14, for example from 14 to 16, such as from 16 to 18, for example from 18 to 20. In one embodiment it is particularly preferred that ñ is in the range of from 5 to 50.

ã is preferably an integer in the range of from 1 to 49, for example from 1 to 25, such as from 25 to 49, for example from 10 to 40, such as from 15 to 35, for example from 1 to 10, such as from 10 to 20, for example from 20 to 30, such as from 30 to 40, for example from 40 to 49, such as from 1 to 5, for example from 5 to 10, such as from 10 to 15, for example from 15 to 20, such as from 20 to 25, for example from 25 to 30, such as from 35 to 40, for example from 40 to 45, such as from 45 to 49.

õ is preferably an integer in the range of from 1 to 49, for example from 1 to 25, such as from 25 to 49, for example from 10 to 40, such as from 15 to 35, for example from 1 to 10, such as from 10 to 20, for example from 20 to 30, such as from 30 to 40, for example from 40 to 49, such as from 1 to 5, for example from 5 to 10, such as from 10 to 15, for example from 15 to 20, such as from 20 to 25, for example from 25 to 30, such as from 35 to 40, for example from 40 to 45, such as from 45 to 49.

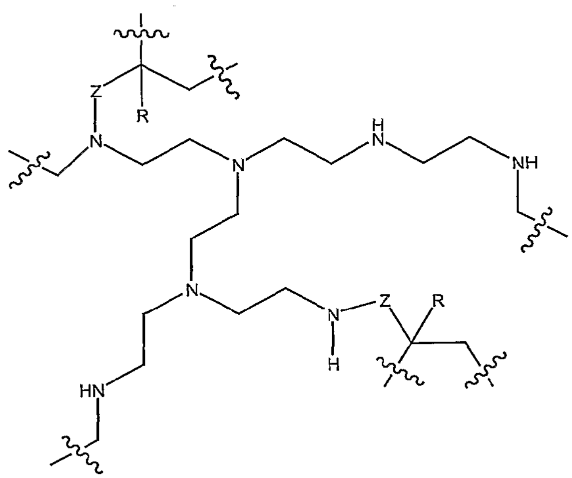
ã or õ can also be 0, but they are preferably not both 0. Accordingly, ã can be zero when õ belongs to any of the ranges listed above and õ can be 0 when ã belongs to any of the ranges listed above.

ã and õ can be selected independently of each other. In one embodiment there is provided a polymer matrix wherein ã is an integer in the range of from 0 to 49, for example from 1 to 25, such as from 25 to 49, for example from 10 to 40, such as from 15 to 35, for example from 0 to 10, such as from 10 to 20, for example from 20 to 30, such as from 30 to 40, for example from 40 to 49, such as from 0 to 5, for example from 5 to 10, such as from 10 to 15, for example from 15 to 20, such as from 20 to 25, for example from 25 to 30, such as from 35 to 40, for example from 40 to 45, such as from 45 to 49, and wherein õ, independently of the value or range of ã,

is an integer in the range of from 0 to 49, for example from 1 to 25, such as from 25 to 49, for example from 10 to 40, such as from 15 to 35, for example from 0 to 10, such as from 10 to 20, for example from 20 to 30, such as from 30 to 40, for example from 40 to 49, such as from 0 to 5, for example from 5 to 10, such as from 10 to 15, for example from 15 to 20, such as from 20 to 25, for example from 25 to 30, such as from 35 to 40, for example from 40 to 45, such as from 45 to 49.

In preferred embodiments, ã can be an integer in the range of from 0 to 10 when õ is an integer in the range of from 0 to 10, such as from 10 to 20, for example from 20 to 30, such as from 30 to 40, for example from 40 to 49; or ã can be an integer in the range of from 10 to 20, when õ is an integer in the range of from 0 to 10, such as from 10 to 20, for example from 20 to 30, such as from 30 to 39; or ã can be an integer in the range of from 20 to 30, when õ is an integer in the range of from 0 to 10, such as from 10 to 20, for example from 20 to 29; or ã can be an integer in the range of from 30 to 40, when õ is an integer in the range of from 0 to 10, such as from 10 to 19; or ã can be an integer in the range of from 40 to 49, when õ is an integer in the range of from 0 to 9.

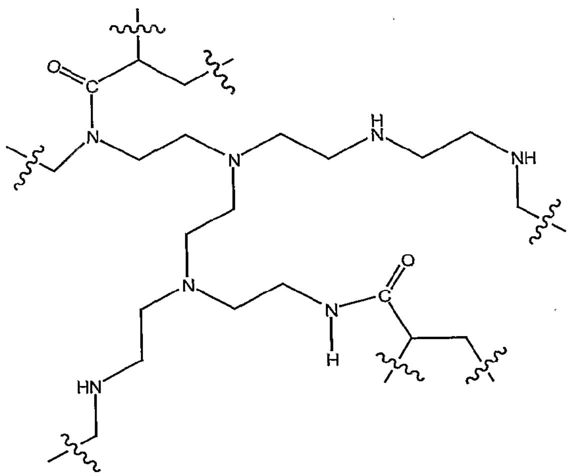
In yet another embodiment there is provided a cross-linked and optionally beaded polymer matrix comprising the structure (formula II)



wherein Z is CO or $COCH_2$ or SO_2 or CS or CNH or Aryl,
wherein R is H or CH_3 or C_2H_5, and

wherein the number of ethyleneimine units is from 5 to 60000, such as from 10 to 120, for example from 121 to 1200, such as from 1201 to 23000, for example from 23001 to 50000.

In a still further embodiment there is provided a polymer matrix comprising the structure (formula IV)



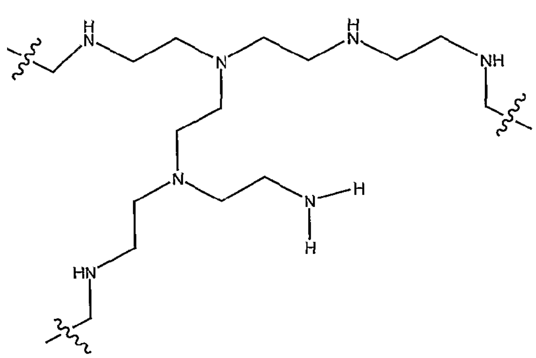
wherein the number of ethyleneimine units is from 5 to 60000, such as from 10 to 120, for example from 121 to 1200, such as from 1201 to 23000, for example from 23001 to 50000.

The polymer matrix preferably comprises at least about 30% (w/w), such as from about 30 to 50 % (w/w), for example from about 50 to 70 % (w/w), such as from about 70 to 90 % (w/w), for example more than 90 % (W/W) of a polyethyleneimine functionalized with at least one fragment comprising a vinyl group, wherein the polymerization of the vinyl group is capable of generating the polymer matrix.

The polymer matrix preferably has a number average molecular weight (M_n) of the polyethyleneimine in the range of from 200 to 60000, such as from 200 to 45000, for example from 200 to 30000, such as from 200 to 25000, for example from 200 to 20000, such as from 200 to 15000, for example from 200 to 10000, such as from 200 to 8000, for example from 200 to 6000, such as from 200 to 5000, for example from 200 to 4500, such as from 200 to 4000, for example from 200 to 3500, such as from 200 to 3000, for example from 200 to 2500, such as from 200 to 2400, for example from 200 to 2300, such as from 200 to 2200, for example from 200 to 2100,

such as from 200 to 2000, for example from 200 to 1900, such as from 200 to 1800, for example from 200 to 1700, such as from 200 to 1600, for example from 200 to 1500, such as from 200 to 1400, for example from 200 to 1300, such as from 200 to 1200, for example from 200 to 1100, such as from 200 to 1000, for example from 200 to 900, such as from 200 to 800, for example from 200 to 700, such as from 200 to 600, for example from 400 to 3000, such as from 400 to 2500, for example from 400 to 2000, such as from 400 to 1800, for example from 400 to 1600, such as from 400 to 1400, for example from 400 to 1200, such as from 400 to 1000, for example from 400 to 800, such as from 400 to 600, for example from 600 to 3000, such as from 600 to 2500, for example from 600 to 2000, such as from 600 to 1800, for example from 600 to 1600, such as from 600 to 1400, for example from 600 to 1200, such as from 600 to 1000, for example from 600 to 800, such as from 800 to 3000, for example from 800 to 2500, such as from 800 to 2000, for example from 800 to 1800, such as from 800 to 1600, for example from 800 to 1400, such as from 800 to 1200, for example from 800 to 1000, such as from 1000 to 3000, for example from 1000 to 2500, such as from 1000 to 2000, for example from 1000 to 1800, such as from 1000 to 1600, for example from 1000 to 1400, such as from 1000 to 1200.

When there is provided a cross-linked and beaded polymer matrix formed from a macromonomer comprising a polyethyleneimine and a polyfunctional alkylating agent, under inverse suspension or inverse emulsion polymerisation conditions, the polyethyleneimine is in one embodiment polydisperse and branched as illustrated by the formula (V)



wherein the number of ethyleneimine units is from 5 to 50000, such as from 10 to 120, for example from 121 to 1200, such as from 1201 to 23000, for example from 23001 to 50000.

The polyfunctional alkylating agent can be of the formula AXq,

wherein A is a saturated or unsaturated aliphatic and/or aromatic, or composed of both saturated and/or unsaturated aliphatic and aromatic fragments, and optionally containing heteroatoms such as silicon, nitrogen, phosphorous, oxygen, or sulphur;

wherein X is a reactive group; and

wherein q, is the number of reactive groups, such as 2, 3, 4, 5, or 6.

A can be an aliphatic or alkylaryl group having 2 to 200 carbon atoms and optionally having 1 to 100 hetero atoms such as nitrogen, oxygen, or sulphur; preferably an aliphatic or alkylaryl group having 10 to 100 carbon atoms and optionally having 2 to 50 hetero atoms such as nitrogen, oxygen, or sulphur.

In one embodiment, A is preferably selected from the group consisting of 1,2-ethylene, 1,3-propylene, 1,4-butylene, 1,4-butenylene, 1,5-pentylene, 1,6-hexylene, *o*-xylylene, *p*-xylylene, oxydiethyl, tri(ethylene oxide)diyl, tetra(ethylene oxide)diyl, penta(ethylene oxide)diyl, hexa(ethylene oxide)diyl, hepta(ethylene oxide)diyl, octa(ethylene oxide), nona(ethylene oxide)diyl, deca(ethylene oxide)diyl, and a polydisperse poly(ethylene oxide)diyl, such as (ethylene oxide)$_{10}$diyl, polydisperse (ethylene oxide)$_{15}$diyl, polydisperse (ethylene oxide)$_{20}$diyl, polydisperse (ethylene oxide)$_{25}$diyl, polydisperse (ethylene oxide)$_{30}$diyl, polydisperse (ethylene oxide)$_{40}$diyl, and polydisperse (ethylene oxide)$_{45}$diyl, or comprises one ore more members of above defined group, including any combination of said group members, and independently thereof, X is selected from S_N2 leaving groups; Michael acceptors; isocyanates; carbonyl groups susceptible to reductive amination, with the option that the cross-linking step is followed by reduction of the imine to the amine, and N-(hydroxyalkyl) groups.

In specific embodiments, X can be selected from chloride, bromide, iodide, methanesulfonate, trifluoromethanesulfonate, p-toluenesulfonate, and epoxide; or from acrylate, methacrylate, ethacrylate and acrylamido; or from alkyl isocyanate and aryl isocyanate, or from aldehydes and ketones susceptible to reductive amina

tion, with the option that the cross-linking step is followed by reduction of the imine to the amine; or X can be a N-(hydroxymethyl) group.

The above-mentioned reducing agent can be any suitable reducing agent, such as a reducing agent comprises a borohydride, such as sodium borohydride or sodium cyanoborohydride, or an aluminium hydride, such as lithium aluminiumhydride, or sodium bis(2-methoxyethoxy)aluminiumhydride.

Examples of AXq are ethylene dibromide, propylene dibromide, butylene dibromide, xylylene dibromide, ethylene glycol ditosylate, diethylene glycol dichloride, triethyleneglycol dichloride, polyethylene glycol dichloride, epichlorohydrine, ethylene glycol diglycidyl ether, diethylene glycol diglycidyl ether, triethylene glycol diglycidyl ether, polydisperse polyethylene glycol diglycidyl ether such as (ethylene oxide)$_{10}$, diglycidyl ether, (ethylene oxide)$_{15}$, diglycidyl ether (ethylene oxide)$_{20}$, diglycidyl ether, ethoxylated trimethylolpropane triglycidyl ether, and ethoxylated dipentaerythritol hexaglycidyl ether.

Further examples of AXq are ethylene glycol diacrylate, diethyleneglycol diacrylate, polyethylene glycol diacylate, polyethyleneglycol dimethacrylate, ethoxylated trimethylolpropane triacrylate, ethoxylated dipentaerythritol hexaacrylate, and Jeffamine diacrylate.

Still further examples of AXq are 1,6-hexane diisocyanate, isophorone diisocyanate, toluene diisocyanate, and 1,4-phenylene diisocyanate.

Even further examples of AXq are formaldehyde, glyoxal, succinaldehyde, glutaraldehyde, 1,4-diformylbenzene, 1,4-diacetylbenzene and polyethylene glycol 1,ω-bis(formylmethyl) ether, with the option that the cross-linking step is followed by reduction of the imine to the amine as described herein above.

Yet further examples of Axq are N,N'-bis(hydroxymethyl)urea and a hydroxymethyl derivative of melamine, such as hexamethylolmelamine.

The amine group loading capacity of the polymer matrix according to the invention can be in the range of from 0.1 to about 23 mmol/gram, for example from 0.1 to 20 mmol/gram, such as from 0.1 to 15 mmol/gram, for example from 0.1 to 10 mmol/gram, such as from 0.1 to 8 mmol/gram, for example from 0.1 to 6 mmol/gram, such as from 0.1 to 5 mmol/gram, for example from 0.1 to 4 mmol/gram, such as from 0.1 to 3 mmol/gram, for example from 0.1 to 2 mmol/gram, such as from 0.2 to 20 mmol/gram, for example from 0.4 to 20 mmol/gram, such as from 0.6 to 20 mmol/gram, for example from 0.8 to 20 mmol/gram, such as from 1.0 to 20 mmol/gram, for example from 2.0 to 20 mmol/gram, such as from 4.0 to 20 mmol/gram, for example from 6.0 to 20 mmol/gram, such as from 8.0 to 20 mmol/gram, for example from 10 to 20 mmol/gram, such as from 12 to 20 mmol/gram, for example from 14 to 20 mmol/gram, such as from 16 to 20 mmol/gram, for example from 18 to 20 mmol/gram, such as from 0.1 to 0.5 mmol/gram, for example from 0.5 to 1.0 mmol/gram, such as from 1.0 to 2.0 mmol/gram, for example from 2.0 to 4.0 mmol/gram, such as from 4.0 to 6.0 mmol/gram, for example from 6.0 to 8.0 mmol/gram, such as from 8.0 to 10 mmol/gram, such as from 10 to 12 mmol/gram, for example from 12 to 14 mmol/gram, such as from 14 to 16 mmol/gram, for example from 16 to 18 mmol/gram.

The swelling volume of the polymer matrix in an aqueous liquid, including water, is preferably in the range of from 1 ml/gram to preferably less than 32 ml/gram, such as from 1 ml/gram to 24 ml/gram, for example from 1 ml/gram to 20 ml/gram, such as from 1 ml/gram to 18 ml/gram, for example from 1 ml/gram to 16 ml/gram, such as from 1 ml/gram to 14 ml/gram, for example from 1 ml/gram to 12 ml/gram, such as from 1 ml/gram to 10 ml/gram, for example from 1 ml/gram to 9 ml/gram, such as from 1 ml/gram to 8 ml/gram, for example from 1 ml/gram to 7 ml/gram, such as from 1 ml/gram to 6 ml/gram, for example from 1 ml/gram to 5 ml/gram, such as from 1 ml/gram to 4 ml/gram, for example from 1 ml/gram to 3 ml/gram, such as from 1 ml/gram to 2 ml/gram, for example from 4 ml/gram to 20 ml/gram, such as from 4 ml/gram to 18 ml/gram, for example from 4 ml/gram to 16 ml/gram, such as from 4 ml/gram to 14 ml/gram, for example from 4 ml/gram to 12 ml/gram, such as

from 4 ml/gram to 10 ml/gram, for example from 4 ml/gram to 8 ml/gram, such as from 4 ml/gram to 6 ml/gram, for example from 6 ml/gram to 20 ml/gram, such as from 6 ml/gram to 18 ml/gram, for example from 6 ml/gram to 16 ml/gram, such as from 6 ml/gram to 14 ml/gram, for example from 6 ml/gram to 12 ml/gram, such as from 6 ml/gram to 10 ml/gram, for example from 6 ml/gram to 8 ml/gram, such as from 8 ml/gram to 20 ml/gram, for example from 8 ml/gram to 16 ml/gram, such as from 8 ml/gram to 12 ml/gram, for example from 2 ml/gram to 4 ml/gram, such as from 8 ml/gram to 10 ml/gram, for example from 10 ml/gram to 12 ml/gram, such as from 12 ml/gram to 14 ml/gram, for example from 14 ml/gram to 16 ml/gram, such as from 16 ml/gram to 18 ml/gram, for example from 18 ml/gram to 20 ml/gram.

The polymer matrix can have a ratio R between i) the amine group loading capacity and ii) the swelling volume of the matrix in an aqueous liquid, including water, in the range of from 0.1 to 20, such as from 0.1 to 18, for example from 0.1 to 16, such as from 0.1 to 14, for example from 0.1 to 12, such as from 0.1 to 10, for example from 0.1 to 9, such as from 0.1 to 8, for example from 0.1 to 7, such as from 0.1 to 6, for example from 0.1 to 5, such as from 0.1 to 4, for example from 0.1 to 3, such as from 0.1 to 2, for example from 0.1 to 1, such as from 0.1 to 0.5, for example from 2 to 20, such as from 2 to 18, for example from 2 to 16, such as from 2 to 14, for example from 2 to 12, such as from 2 to 10, for example from 2 to 8, such as from 2 to 6, for example from 2 to 4, such as from 1 to 10, for example from 10 to 20, such as from 1 to 4, for example from 4 to 8, such as from 8 to 12, for example from 12 to 16, such as from 16 to 20.

In some preferred embodiments, the polymer matrix can attain a beaded or spherical form, preferably with an average diameter in the range of from 0.1 μm to preferably less than 1000 μm. The beaded, cross-linked polymer matrix can be formed by polymerisation of droplets in an inert phase, such as unreactive oil, for example silicon oil, it can be formed formed by bulk polymerisation, by reverse suspension polymerisation, or by spray polymerisation.

When there is provided a cross-linked and beaded polymer matrix formed from a macromonomer comprising a polyethyleneimine and a polyfunctional alkylating agent, under inverse suspension or inverse emulsion polymerisation conditions,

there is also provided a method for generating such a matrix, said method comprising the steps of:

a) providing a polyethyleneimine of formula V, wherein the number of ethyleneimine units is from 5 to 60000, such as from 10 to 120, for example from 121 to 1200, such as from 1201 to 23000, for example from 23001 to 50000,

b) providing and a cross-linking molecule AXq, wherein A is a saturated or unsaturated aliphatic and/or aromatic, or composed of both saturated and/or unsaturated aliphatic and aromatic fragments, and optionally containing heteroatoms such as silicon, nitrogen, phosphorous, oxygen, or sulphur; wherein X is a reactive group; and wherein q, is the number of reactive groups, such as 2, 3, 4, 5, or 6,

c) reacting under beading conditions the polyethyleneimine provided in step a) with the the cross-linking molecule AXq provided in step b), and

d) obtaining a cross-linked and beaded polymer matrix according to the invention.

The polyethyleneimine of formula V can be mixed with AXq in the presence of a surface active agent. The surface active agent can be added to the reactive phase and/or to the non-reactive phase, and the reaction mixture can be added with stirring or ultrasonification to a liquid not miscible with the reactive mixture, preferably in a predetermined specific ratio and at a temperature at which the bead formation and cross linking is fast.

The surface active agent can be selected from the group consisting of negatively charged surface active agent such as sodium laurate, sodium lauryl sulfate, sodium laurylsulfonate, and sodium decylbenzenesulfonate; or from the group consisting of neutral surface active agent such as ethoxylated aliphatic alcohols, ethoxylated alkylphenols, alkylphenols, carbohydrate derived esters, e.g., sorbitan laurate, amphiphilic polymers such as copolymers of polyethylene glycol methacrylate and lauryl acrylate or trialkylsilylalkyl methacrylate or copolymers of ethylene oxide and propylene oxide, and homopolymers, such as polyvinyl acetate or completely or partially hydrolysed polyvinyl acetate; or from the group consisting of positively charged sur

face active agents such as hexadecyltrimethylammonium bromide, tetraheptylammoinum chloride and tetrabutylammonium bromide.

The non-miscible liquid can be a petroleum fraction, an aliphatic oil, a natural fat or triglyceride, an aromatic solvent such as toluene or xylene, a halogenated solvent such as methylene chloride, chloroform, carbon tetrachloride, dichloroethane, trichloroethylene, chlorobenzene, a fluorinated solvent, or mixtures thereof. The ratio of the reactive phase and the nonmiscible liquid can be from 2:1 to 1:100, such as from 4:5 to 1:75, for example from 1:2 to 1:30.

A nucleophilic catalyst or a basic catalyst can also be present. The nucleophilic catalyst can be a salt such as sodium bromide, sodium iodide, potassium iodide, or tetrabutylammonium bromide, and the basic catalyst can be an alkaline compound such sodium hydrogen carbonate, potassium carbonate, potassium hydroxide, or tetrabutylammonium hydroxide.

The stoechiometry of the reactants is defined by the molar ratio of nitrogens of the polyethyleneimine of formula V to X of AX_q (mol N/mol X) is 500 to 0.1, for example from 100 to 0.5, such as from 50 to 0.9.

The reaction can be run neat or in the presence of a solvent. When run in the presence of a solvent, the solvent is preferably selected from water, methanol, ethanol, ethylene glycol, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidone, or acetonitrile.

The concentration of the reaction solution can be from 5 to 100%, such as from 10 to 80%, for example from 20 to 60%, the stirring frequency can be from 1 to 2000 rpm, for example from 50 to1000 rpm, for example from 100 to 500 rpm, such as from 200 to 400 rpm, and the reaction temperature can be from –20°C to 150°C, such as from 20°C to 100°C, for example from 40°C to 80°C.

When the cross-linked polymer matrix is formed from a macromonomer comprising a polyethyleneimine functionalized with at least one fragment comprising a vinyl group, wherein said fragment can be polymerized using radical or ionic initiators to form the cross-linked polymer matrix, the invention also pertains to a method for preparing such a polymer matrix, optionally in beaded form, said method comprising the step of providing a macromonomer comprising a polyethyleneimine functionalized with at least one fragment comprising a vinyl group, and polymerising the vinyl groups of said macromonomers using radical or ionic initiators to form the cross-linked polymer matrix.

In one aspect there is provided a method for preparing the polymer matrix according to the invention, such as, but not limited to polymer matrices comprising the structures illustrated by any of the formulas I, II and III, optionally in beaded form, said method comprising the steps of

a) providing a macromonomer comprising a polyethyleneimine functionalized with at least one fragment comprising a vinyl group, and

b) polymerising the vinyl groups of said macromonomers using radical or ionic initiators to form the cross-linked polymer matrix.

The above method can comprise the further step of chemically reducing the primary amide functionalities and thereby generate a resin wherein at least the majority of the primary amide functionalities are reduced to secondary amine functionalities.

There is also provided a composition comprising a plurality of beaded, cross-linked polymers according to the invention, wherein preferably the average diameter is in the range of from 0.1 μm to preferably less than 1000 μm.

In a still further embodiment there is provided a functional surface comprising a polymer matrix according to the invention, and attached thereto at least one functional moiety. such as e.g. a bioactive species preferably selected from RNA, DNA, a peptide, and an amino acid residue. The surface can additionally comprise a linker residue. The functional surface is preferably solid.

There is also provided the use of the polymer matrix according to the invention for a support for the synthesis of an organic molecule, for for scavenging excess acyl compounds from a composition comprising a mixture of molecular entities, such as e.g. entities resulting from amine reactions and acylation reactions.

Additional uses of the polymer matrix includes a use for scavenging excess carbonyl compounds from a composition comprising a mixture of molecular entities, such as entities resulting from organometallic reagent addition reactions and carbonyl compound addition reactions.

Still further uses of the polymer matrix are for solid phase enzyme reactions, as a support for combinatorial chemistry, as a support for the synthesis of a peptide, a protein, a DNA, and a RNA, for protein immobilisation, as well as chromatographic separation or purification, including affinity purification.

In another embodiment there is provided the use of a partially acryloylated polyethylenimine in the preparation of a beaded, cross-linked polymer matrix according to the invention, preferably by inverse suspension polymerization.

There is also provided the use of the polymer matrix according to the invention for scavenging metals ions, such as metal ions in the form of bi-products in organometallic reactions, metal ions in effluent water, such as sewage water, and metal ions from ore or metal scrap.

The metal can be selected from metals in periods 4 and 5 of the periodic system, including the Lanthanides; and from metals in period period 6 of the periodic system, including the Actinides. Preferably, the metal is palladium or cupper.

There is also provided a functional surface, such as a solid functional surface comprising a polymer matrix according to the invention and attached thereto at least one functional moiety, such as e.g. a bioactive species preferably selected from RNA, DNA, a peptide, and an amino acid residue. The functional surface can further comprise a linker residue.

In preferred embodiments, the functional surface is obtained by converting at least some of the amino groups of the polymer matrix according to the invention after polymerisation and beading of the polymer matrix, thereby generating a functional surface of the structure

(polymer matrix)–NR^1R^2,

or a functional surface of the structure

(polymer matrix)–NR^3–(polymer matrix),

wherein R^1, R^2 and R^3 are independently H, or an organic group formed by reaction of the amino groups of the polymer matrix according to any of claims 1 to 64 with an alkylating agent or an acylating agent.

The alkylating agent is preferably selected from an alkyl halide or a substituted alkyl halide, or from an alkyl sulphonate or a substituted alkyl sulphonate.

The alkylating agent can also be is an epoxide.

In some preferred embodiments the alkylating agents are described herein above in connection with the polymer matrix formed from a macromonomer comprising a polyethyleneimine and a polyfunctional alkylating agent, under inverse suspension or inverse emulsion polymerisation conditions.

The alkylation agent can be selected from methyl iodide, ethyl iodide, propyl bromide, butyl bromide, chloroacetic acid, benzyl chloride, benzyl bromide, methylbenzyl bromide, methoxybenzyl bromide, and nitrobenzyl bromide; from methyl methanesulphonate, methyl trifluoromethanesulphonate and methyl p-toluenesulphonate; from ethylene oxide, propylene oxide and a glycidol derivative; or from methyl acrylate and ethyl acrylat.

The acylating agent can be selected from a carboxylic acid, an activated carboxylic acid, a carbonic acid derivative and a heteroallene, from formic acid, acetic acid, propionic acid, benzoic acid, mercaptoacetic acid, 3-mercaptopropanoic acid, thiolactic acid, and protected aminoacids, such as N-(fluorenyloxymethylcarbonyl)glycine or N-(benzyloxycarbonyl)alanine, or N-(*t*-butoxycarbonyl)phenylalanine, or derivatives thereof, optionally activated by condensing agents such as dicyclohexylcarbodiimide; from acetic anhydride, acetyl chloride, ethyl acetate and benzoyl chloride; from methyl chloroformate, *t*-butyl chloroformate, benzyl chloroformate and diphenyl carbonate; from ethyl isocyanate, phenyl isocyanate, ethyl isothiocyanate and phenyl isothiocyanate.

There is also provided a method for preparing a functional surface according to the invention, said method comprising the steps of i) cross-linking a plurality of partially acryloylated polyethylenimines, and ii) contacting said functional surface comprising said cross-linked partially acryloylated polyethylenimines with at least one functional moiety.

In a still further aspect there is provided a method for targeting a functional moiety attached to a functional surface, said method comprising the steps of i) providing a functional surface according to the invention, and ii) targeting said functional moiety with at least one targeting species having an affinity for said functional moiety.

Accordingly, the invention also relates to a method for identifying and/or purifying a targeting species having an affinity for a functional moiety, said method comprising the steps of i) providing a functional surface according to the invention, and ii) targeting said functional moiety with at least one targeting species having an affinity for said functional moiety, and iii) identifying and/or purifying the at least one targeting species having an affinity for said functional moiety. The invention also relates to targeting species identified by the aforementioned method.

There is also provided a method for therapy of a human or animal body, said method comprising the step of administering to said human or animal body in a pharmaceutical effective amount a targeting species identified as described herein above.

Examples

The invention is further exemplified herein below without being limited to the resins and methods disclosed.

Example 1: Synthesis of partially acryloylated polyethylenimine

Reagents were obtained from Aldrich and used without any purification. All solvents used were of HPLC grade kept over molecular sieves. Polymerisation was performed in a 250 ml glass reactor equipped with a three blade stirrer.

Acryloyl chloride (2.403 ml, 36 mmol) in DCM (12 ml) was added dropwise to a solution of polyethylenimine (7.9 ml, 20 mmol) in DCM (18 ml) at 0 °C with stirring. The reaction mixture was kept for 1 h at 20 °C. The DCM was evaporated and drying in vacuo at 20 °C yielded the 90% acyloylated polyethylenamine as pale yellow coloured thick oil.

Example 2: Synthesis of ULTRAMINE

a. Bulk polymerisation

$(Acr)_{1.8}$-Polyethylenimine (5 g, 9.58 mmol) in water (5 ml) and free radical initiator ammonium persulfate (250 mg) in water (1 ml) were taken in a RB flask. The reaction mixture was kept in a thermostated oil bath maintained at 70 °C for 30 min. the white, hard bulky polymer obtained was washed with water (6 × 15 ml), MeOH (6 × 15 ml), EtOH (6 × 15 ml), DMF (6 × 15 ml), DCM (6 × 15 ml). The polymer was granulated by pushing through a 1 mm net and sieved.

b. Inverse suspension polymerisation

(a) ULTRAMINE was prepared by inverse suspension polymerisation method. A mixture of n-heptane-carbon tetrachloride (6:4, v/v, 140 ml) was used as the continuous phase and added to the polymerisation flask kept in an oil bath at 70° C. The solution was purged with argon for 10 min and stirred at a rate of 650 rpm. In a typical synthesis procedure, a solution of $(Acr)_{1.8}$-polyethylenimine (10 g, 19.16 mmol) in water (25 ml) was degassed with argon for 30 min. A solution of sorbitan monolaurate (0.5 ml) in DMF (1 ml) and the free radical initiator ammonium persulfate

(500 mg) in water (2 ml) were added to the monomer mixture. The reaction mixture was then rapidly added to the suspension medium stirred at 650 rpm at 70 °C. After one min, TEMED (1 ml) was added to the reactor. The reaction was allowed to continue for 3h, the beads formed were filtered through the sieves, washed thoroughly with ethanol (10×), water (10×), ethanol (10×) and dried under high vacuum.

(b) n-heptane (140 ml) was used as the continuous phase and added to the polymerisation flask kept in an oil bath at 70° C. The solution was purged with argon for 10 min and stirred at a rate of 650 rpm. In a typical synthesis procedure, a solution of $(Acr)_{1.8}$-polyethylenimine (10 g, 19.16 mmol) in water (25 ml) was degassed with argon for 30 min. A solution of sorbitan monolaurate (0.5 ml) in DMF (1 ml) and the free radical initiator ammonium persulfate (500 mg) in water (2 ml) were added to the monomer mixture. The reaction mixture was then rapidly added to the suspension medium stirred at 650 rpm at 70 °C. After one min, TEMED (1 ml) was added to the reactor. The reaction was allowed to continue for 3h, the beads formed were filtered through the sieves, washed thoroughly with ethanol (10×), water (10×), ethanol (10×) and dried under high vacuum.

(c) Isopar M (140 ml) was used as the continuous phase and added to the polymerisation flask kept in an oil bath at 70° C. The solution was purged with argon for 10 min and stirred at a rate of 650 rpm. In a typical synthesis procedure, a solution of $(Acr)_{1.8}$-polyethylenimine (10 g, 19.16 mmol) in water (25 ml) was degassed with argon for 30 min. A solution of sorbitan monolaurate (0.5 ml) in DMF (1 ml) and the free radical initiator ammonium persulfate (500 mg) in water (2 ml) were added to the monomer mixture. The reaction mixture was then rapidly added to the suspension medium stirred at 650 rpm at 70 °C. After one min, TEMED (1 ml) was added to the reactor. The reaction was allowed to continue for 3h, the beads formed were filtered through the sieves, washed thoroughly with ethanol (10×), water (10×), ethanol (10×) and dried under high vacuum.

(d) Isopar M (140 ml) was used as the continuous phase and added to the polymerisation flask kept in an oil bath at 30° C. The solution was purged with argon for 10 min and stirred at a rate of 650 rpm. In a typical synthesis procedure, a solution of $(Acr)_{1.8}$-polyethylenimine (10 g, 19.16 mmol) in water (25 ml) was degassed with argon for 30 min. A solution of sorbitan monolaurate (0.5 ml) in DMF (1 ml) and the

free radical initiator ammonium persulfate (500 mg) in water (2 ml) were added to the monomer mixture. The reaction mixture was then rapidly added to the suspension medium stirred at 650 rpm at 30°C. After one min, sodium disulfite (50 mg) in water (1 ml) and TEMED (1 ml) were added simultaneously but separately to the reactor. The reaction was allowed to continue for 3h, the beads formed were filtered through the sieves, washed thoroughly with ethanol (10×), water (10×), ethanol (10×) and dried under high vacuum.

Example 3: Characterisation of synthesised ULTRAMINE resins

The synthesised ULTRAMINE resins were characterised as described herein below.

Loading:

The amino functional loading was determined from the Fmoc-derivatised resin. The resin (3-5 mg) was treated with piperidine-MeOH solution (20% v/v, 8 ml) for 30 min. The amino capacity of the resin was calculated from the OD value of piperidine-dibenzofulvene solution at 290 nm. The amino functional loading of the ULTRAMINE is measured as 16.8 mmol/g.

Swelling:

The swelling capability of the resin in different solvents were determined by the syringe method. In a typical procedure, the resin (100 mg) was taken in a 2 ml syringe fitted with a Teflon filter at the bottom. The solvent was sucked in to the syringe and after 3 h, excess solvent was removed by applying force on the piston. The extent of swelling of the resin in each solvent was determined from the volume of the resin before and after the solvent incubation.

Chemical stability:

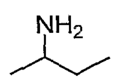
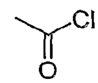
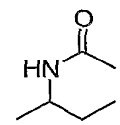
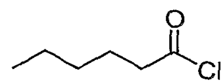
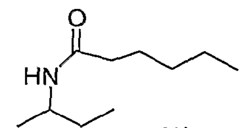
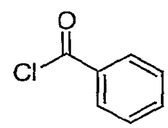
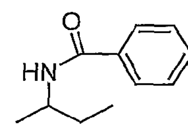
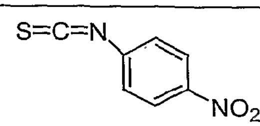
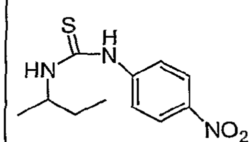
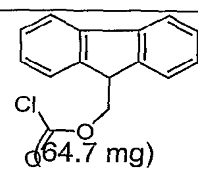
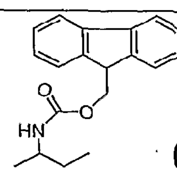
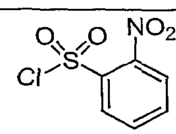
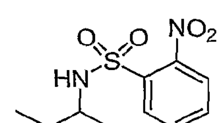
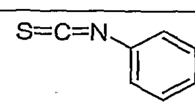
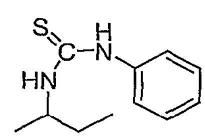
The stability studies of the resin were carried out in different reagents like trifluoro acetic acid (100%), 20% piperidine in DMF, DBU (100%), butyl lithium (2.7 M solution in heptane, 100%), triflic anhydride (100%), saturated NaOH, and BF_3 Et_2O (100%). The resin samples (100 mg) were separately stirred with the reagents. After 48 h, the resin was filtered washed dried and IR spectra were recorded and compared with original. The swelling properties of the resin after treatment of the reagents for two weeks were also compared. The resin did not dissolve in any of these

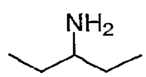
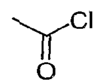
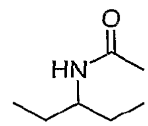
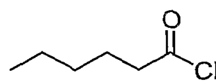
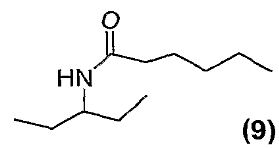
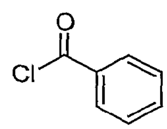
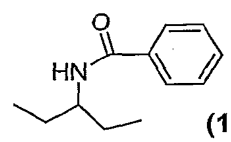
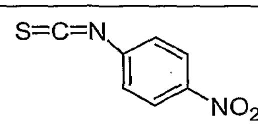
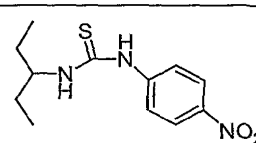
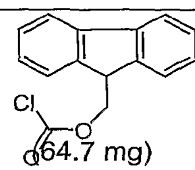
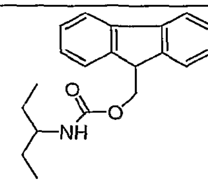
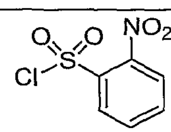
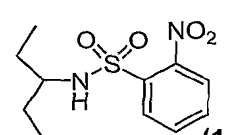
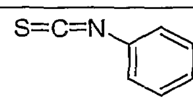
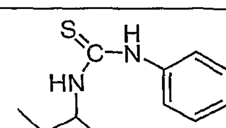
conditions and showed no changes in colour or swelling indicating no bond cleavage.

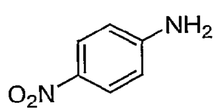
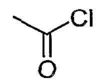
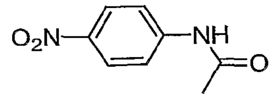
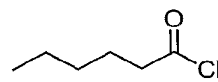
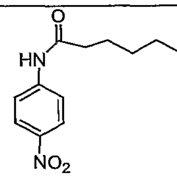
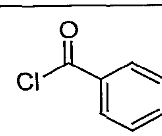
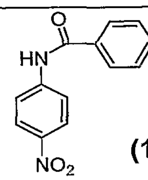
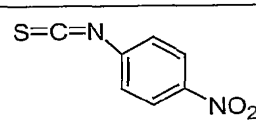
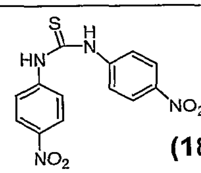
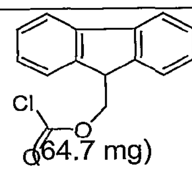
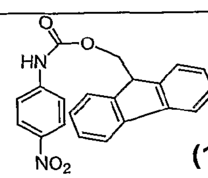
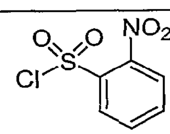
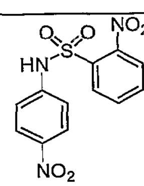
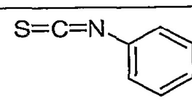
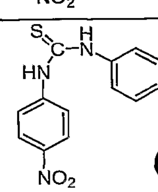
General procedure for acylation

All the compounds were synthesised in a parallel scheme (Table 1). To each 10 ml plastic vial containing amine (0.1 mmol) in dry DCM (1 ml), add acylating reagent (0.25 mmol). Each vial was closed tightly, and the mixture was agitated at rt with a shaker for 16 h. ULTRAMINE (50 mg) was added to each vial and the solution was diluted to 3 ml using DCM. The resulting mixture was then agitated for 6 h at rt and filtered. The resin was washed with DCM (4 × 4 ml).

The combined filtrate and washings were concentrated and transferred to a vial, and the solvent was evaporated by a stream of argon. The resulting product was dried in vacuum overnight. The purity of each product was analysed by HPLC.

Entry	Amine (0.1 mmol)	Acylating agent (0.25 mmol)	Products
1	 (10.2 µl)	 (17.8 µl)	 **(1)**
2		 (34.2 µl)	 **(2)**
3		 (29.1 µl)	 **(3)**
4		 (45 mg)	 **(4)**
5		 (64.7 mg)	 **(5)**
6		 (55.4 mg)	 **(6)**
7		 (30 µl)	 **(7)**

Entry	Amine (0.1 mmol)	Acylating agent (0.25 mmol)	Products
8	 (11.7 µl)	 (17.8 µl)	 **(8)**
9		 (34.2 µl)	 **(9)**
10		 (29.1 µl)	 **(10)**
11		 (45 mg)	 **(11)**
12		 (64.7 mg)	 **(12)**
13		 (55.4 mg)	 **(13)**
14		 (30 µl)	 **(14)**

Entry	Amine (0.1 mmol)	Acylating agent (0.25 mmol)	Products
15	 (13.8 mg)	 (17.8 µl)	 **(15)**
16		 (34.2 µl)	 **(16)**
17		 (29.1 µl)	 **(17)**
18		 (45 mg)	 **(18)**
19		 (64.7 mg)	 **(19)**
20		 (55.4 mg)	 **(20)**
21		 (30 µl)	 **(21)**

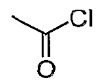
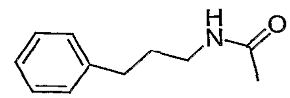
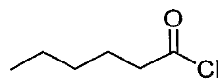
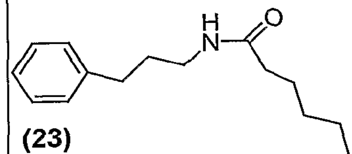
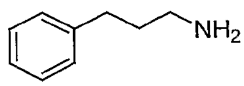
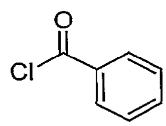
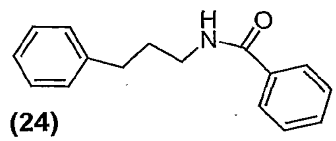
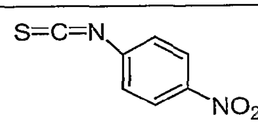
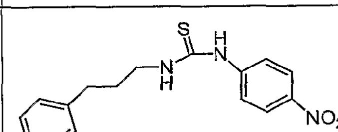
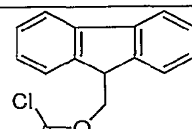
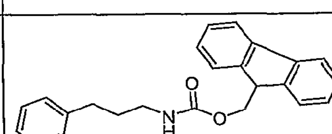
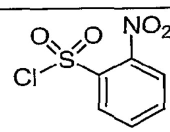
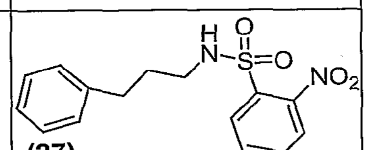
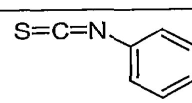
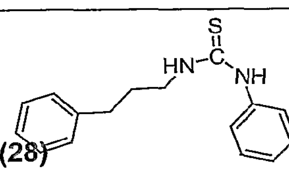
Entry	Amine (0.1 mmol)	Acylating agent (0.25 mmol)	Products
22		 (17.8 µl)	 **(22)**
23		 (34.2 µl)	 **(23)**
24		 (29.1 µl)	 **(24)**
25	(14.3 µl)	 (45 mg)	 **(25)**
26		 (64.7 mg)	 **(26)**
27		 (55.4 mg)	 **(27)**
28		 (30 µl)	 **(28)**

Table 1: The reactions selected for scavenging excess acylating agent with

ULTRAMINE

Entry	Amine	Acylating agent	Product	% mass yield/ HPLC purity
1	Sec-Butylamine	Acetyl chloride	**1**	99.7/100
2	Sec-Butylamine	Hexanoyl chloride	**2**	99.0/98.5
3	Sec-Butylamine	Benzoyl chloride	**3**	99.2/100
4	Sec-Butylamine	4-nitrophenyl isothiocyanate	**4**	98.3/96.0
5	Sec-Butylamine	Fmoc-Cl	**5**	97.5/94.6
6	Sec-Butylamine	2-nitrophenyl sulfonyl chloride	**6**	98.5/95.3
7	Sec-Butylamine	Phenyl isothiocyanate	**7**	99.3/100
8	1-Ethyl propyl amine	Acetyl chloride	**8**	99.5/100
9	1-Ethyl propyl amine	Hexanoyl chloride	**9**	98.3/100
10	1-Ethyl propyl amine	Benzoyl chloride	**10**	94.8/100
11	1-Ethyl propyl amine	4-nitrophenyl isothiocyanate	**11**	92.8/95.4
12	1-Ethyl propyl amine	Fmoc-Cl	**12**	90.7/94.1
13	1-Ethyl propyl amine	2-nitrophenyl sulfonyl chloride	**13**	93.8/95.6
14	1-Ethyl propyl amine	Phenyl isothiocyanate	**14**	98.9/100
15	4-Nitro aniline	Acetyl chloride	**15**	99.5/100
16	4-Nitro aniline	Hexanoyl chloride	**16**	97.2/100
17	4-Nitro aniline	Benzoyl chloride	**17**	96.1/100
18	4-Nitro aniline	4-nitrophenyl isothiocyanate	**18**	92.4/94.9
19	4-Nitro aniline	Fmoc-Cl	**19**	96.3/93.3

20	4-Nitro aniline	2-nitrophenyl sulfonyl chloride	**20**	97.2/94.2
21	4-Nitro aniline	Phenyl isothiocyanate	**21**	99.2/100
22	3-Phenyl-1-propyl amine	Acetyl chloride	**22**	99.5/100
23	3-Phenyl-1-propyl amine	Hexanoyl chloride	**23**	97.4/100
24	3-Phenyl-1-propyl amine	Benzoyl chloride	**24**	95.8/100
25	3-Phenyl-1-propyl amine	4-nitrophenyl isothiocyanate	**25**	94.0/95.6
26	3-Phenyl-1-propyl amine	Fmoc-Cl	**26**	92.4/92.3
27	3-Phenyl-1-propyl amine	2-nitrophenyl sulfonyl chloride	**27**	94.1/92.7
28	3-Phenyl-1-propyl amine	Phenyl isothiocyanate	**28**	98.3/100

Table 2. Mass yields and purities of solution-phase amides, ureas, carbamates, thioureas, and sulfonamides purified by ULTRAMINE.

Example 4: Synthesis of ULTRAMINE with different cross-linking densities

The polymerizations were performed in n-heptane (140 mL). Sorbitan monolaurate (0.5 mL in DMF) was used as the suspension stabilizer and ammonium persulfate (0.5 g) in water (2 mL) as the free radical initiator. Degassed solution of partially acryloyated polyethylene imine in water (25 mL) was mixed with suspension stabilizer and radical initiator and transferred to the degassed continuous phase stirred at 650 rpm and 70°C. The promoter TEMED (1 mL) was added to the reaction mixture after 1 min, and the reaction was allowed continue for 3h. The beads were filtered and washed thoroughly with ethanol (10×), water (10×) and ethanol (10×). The resin was suspended in 10% DIPEA in ethanol for 4 h, and washed with ethanol (10×), water (10×), ethanol (10×) and dried under high vacuum.

$(Acr)_{13.5\%}$ polyethylene imine (9.8 g, 19.2 mmol) yielded 8.9 g resin (91%). Bead size distribution: 300-500 μm (85%), 100-300 μm (12%), <100 μm (3%); colour: transparent pale yellow; amino loading: 17.3 mmol/g; swelling (ml/g): water (8.5), DMF (4.9).

IR (ν, cm^{-1}) 3272.2 (NH str), 2937.3 (CH str), 1622.3 (CONH).

$(Acr)_{11.5\%}$ polyethylene imine (9.3 g, 18.6 mmol) yielded 8.1 g resin (87%). Bead size distribution: 300-500 μm (87%), 100-300 μm (10%), <100 μm (3%); colour: transparent pale yellow; amino loading: 17.9 mmol/g; swelling (ml/g): water (8.7), DMF (5.1).

IR (ν, cm^{-1}) 3272.2 (NH str), 2937.6 (CH str), 1622.2 (CONH)

$(Acr)_{10\%}$ polyethylene imine (10 g, 20.45 mmol) yielded 8 g resin (80%). Bead size distribution: 300-500 μm (85%), 100-300 μm (10%), <100 μm (5%); colour: transparent pale yellow; amino loading: 18.6 mmol/g; swelling (ml/g): water (9.0), DMF (5.5).

IR (ν, cm^{-1}) 3272.2 (NH str), 2937.3 (CH str), 1622.5 (CONH)

Example 5: Synthesis of ULTRAMINE-Red

The resin (500 mg, 1.6 mmol carbonyl group) and boric acid (0.6 g, 9.6 mmol, 6 equiv) were measured in to a reaction vessel. Trimethyl borate (1 mL, 9.6 mmol, 6 equiv) was added followed by the addition of 1M borane-THF complex (32 mL, 20 equiv). After cessation of hydrogen evolution, the tubes were capped tightly and kept in an oil bath at 65°C for 72 h. The resin was then filtered, washed with DMF (10 mL × 4) and MeOH (10 mL × 4). The resin was then suspended in piperidine (100%, 10 mL) and heated at 65°C for 20 h to disproportionate the borane complexes. Following the decantation of the piperidine-borane solution, the resin was washed with DMF (10 mL × 4), DCM (10 mL × 4) and MeOH (10 mL × 4) and dried under vacuum to provide ULTRAMINE-Red with a quantitative conversion of amide to amine as monitored by the complete disappearance of the carbonyl bands in IR spectrum (Loadings are given in Table 3).

IR (ν, cm^{-1}) 3272.3 (NH str), 2937.6 (CH str) (Fig. 10)

Compressive modulus: 0.45 MPa; colour: transparent pale yellow.

% of acryloylation	Loading (mmol/g)	
	before reduction	after reduction
15	16.5	18.6
13.5	17.3	19.5
11.5	17.9	20.4
10	18.6	21.0

Table 3. Functional loading of ULTRAMINE before and after exhaustive reduction with borane.

Example 6: Synthesis of $ULTRAMINE_{1300}$

$ULTRAMINE_{1300}$ was prepared by inverse suspension polymerization method. n-Heptane (140 mL) was used as the continuous phase and added to the polymerization flask kept in an oil bath at 70° C. The solution was purged with argon for 10 min and stirred at a rate of 650 rpm. In a typical synthesis procedure, a solution of $(Acr)_{10\%}$-polyethylene imine (6 g) in water (25 mL) was degassed with argon for 30 min. A solution of sorbitan monolaurate (0.5 mL) in DMF (1 mL) and the free radical initiator ammonium persulfate (0.5 g) in water (2 mL) were added to the monomer mixture. The reaction mixture was then rapidly added to the suspension medium stirred at 650 rpm at 70 °C. After one min, TEMED (1 mL) was added to the reactor. The reaction was allowed to continue for 3h, the beads formed were filtered through sieves. They were washed thoroughly with ethanol (10×), water (10×) and ethanol (10×). The resin was suspended in 10% DIPEA in ethanol for 4 h, and washed with ethanol (10×), water (10×), ethanol (10×) and dried under high vacuum.

Yield = 5.7 g (95%); bead size distribution: >500 μm (2%), 300-500 μm (80%), 100-300 μm (15%), <100 μm (3%); colour: transparent pale yellow; swelling (ml/g): water (12.2), DMF (8.2).

IR (ν, cm^{-1}) 3272.1 (NH str), 2937.4 (CH str), 1622.2 (CONH)

Example 7: Palladium scavenging.

Palladium complexes and salts are used widely as catalysts in organic synthesis, and are also present in a range of industrial process streams. Due to its environ

mental effects and high cost there is a widespread interest in removing and recovering palladium ions.

In order to demonstrate the ability of the polyamine resins to scavenge palladium ions a range of experiments were undertaken as in the experiments below. The first experiment is demonstrating the capacity of the resin, whereas the other is demonstrating the ability to remove trace elements.

In the first experiment, 2% (W/W) Palladium(II)chloride dissolved in 4 M hydrochloric acid was diluted 1:4 in 50% ethanol in water. 2 ml of the resulting solution containing 8 mg of palladium(II)chloride was added to 10 mg (dry weight) cross linked polyethyleneimine from example(x). The mixture was shaken intermittedly during 1 hour and the visual absorptions spectrum was compared with a reference sample of the 2% stock solution diluted 100 times. The reference sample showed an absorption of 0.29Au at 470 nm, whereas the scavenged sample showed an absorption of 0.40 Au, which can be converted to a concentration of 270 ppm. Thus, just 10 mg of resin was able to remove 7.5mg (or 94%) of palladium content in the sample.

In the second experiment, a 100 times diluted sample of the 2% solution was treated with 10 mg of resin in the manner described above. The resulting sample showed an absorption at 470 nm of 0.01 Au (near the detection limit), corresponding to a concentration below 6 ppm.

Thus it has been shown that a sequential treatment of a palladium solution with the polyamine resins will be able to scavenge palladium down to ppm levels retaining a capacity above 30%. Even better efficiency can be expected in column treatments.

Claims

1. A cross-linked polymer matrix selected from the group consisting of

i) cross-linked polymer matrices formed from a macromonomer comprising a polyethyleneimine functionalized with at least one fragment comprising a vinyl group, wherein said fragment can be polymerized using radical or ionic initiators to form the cross-linked polymer matrix, and

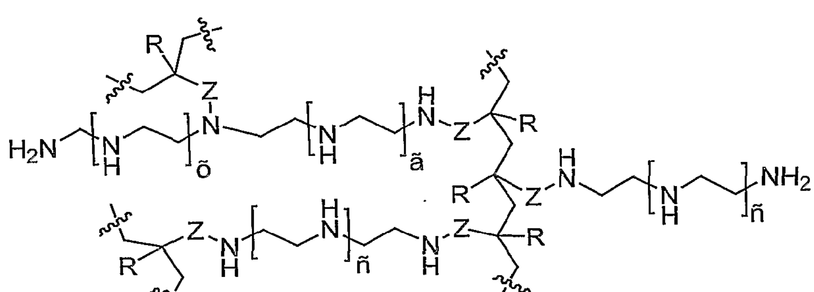
ii) cross-linked and beaded polymer matrices formed from a macromonomer comprising a polyethyleneimine and a polyfunctional alkylating agent, under inverse suspension or inverse emulsion polymerisation conditions.

2. The cross-linked polymer matrix according to claim 1 formed from a macromonomer comprising a polyethyleneimine functionalized with at least one fragment comprising a vinyl group, wherein said fragment can be polymerized using radical or ionic initiators to form the cross-linked polymer matrix.

3. The cross-linked polymer matrix according to any of claims 1 and 2, wherein the polyethyleneimine and the vinyl group is linked by a unit Z selected from a carbonyl group, a sulfone group, an aryl group, and derivatives thereof.

4. The cross-linked polymer matrix according to claim 3, wherein the unit Z is selected from the group consisting of CO; CO-$(CH_2)_m$; SO_2; CS; and CNH; C_6H_4; C_6H_4-CO-$(CH_2)_m$, where $0 \leq m \leq 10$.

5. The cross-linked polymer matrix according to any of claims 1 to 3 comprising the structure (formula I)

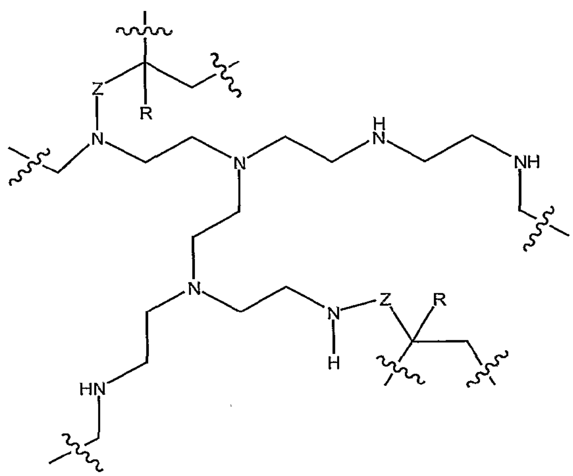


Z= CO or $COCH_2$ or SO_2 or CS or CNH or Aryl
R= H or CH_3 or C_2H_5

ñ is a real number in the range of from 5 to 1500

ã and õ are real numbers in the range of from 0 to ñ

6. The cross-linked polymer matrix according to any of claims 1 to 3, optionally in beaded form, comprising the structure (formula II)



wherein Z is CO or $COCH_2$ or SO_2 or CS or CNH or Aryl,

wherein R is H or CH_3 or C_2H_5, and

wherein the number of ethyleneimine units is from 5 to 60000, such as from 10 to 120, for example from 121 to 1200, such as from 1201 to 23000, for example from 23001 to 50000.

7. The polymer matrix according to any of claims 5 and 6, wherein Z is CO.

8. The polymer matrix according to any of claims 5 and 6, wherein Z is $COCH_2$.

9. The polymer matrix according to any of claims 5 and 6, wherein Z is SO_2.

10. The polymer matrix according to any of claims 5 and 6, wherein Z is CS.

11. The polymer matrix according to any of claims 5 and 6, wherein Z is CNH.

12. The polymer matrix according to any of claims 5 and 6, wherein Z is the aryl C_6H_4-CO-$(CH_2)_m$, where $0 \leq m \leq 10$.

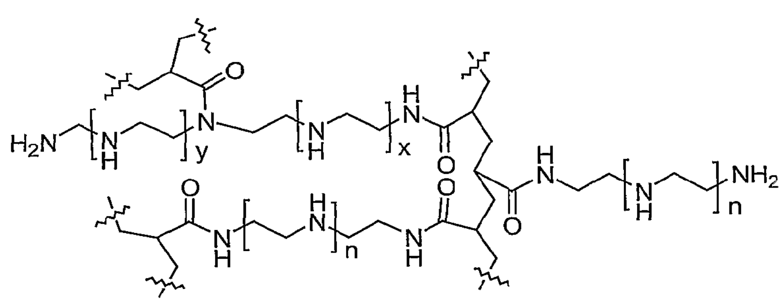
13. The polymer matrix according to any of claims 7 to 12, wherein R is H, CH_3, or C_2H_5.

14. The polymer matrix according to claim 13, wherein R is H.

15. The polymer matrix according to claim 13, wherein R is CH_3.

16. The polymer matrix according to claim 13, wherein R is C_2H_5.

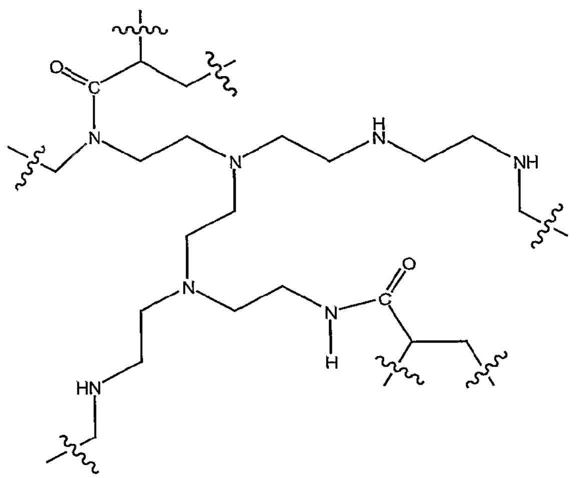
17. The polymer matrix according to any of claims 1 to 16 comprising the structure (formula III)



wherein n is an integer in the range of from 5 to 1500, and

wherein the sum of x and y is an integer of more than 0 and at the most n-1.

18. The polymer matrix according to any of claims 1 to 16 comprising the structure (formula IV)



wherein the number of ethyleneimine units is from 5 to 60000, such as from 10 to 120, for example from 121 to 1200, such as from 1201 to 23000, for example from 23001 to 50000.

19. The polymer matrix according to any of claims 5 and 7 to 17, wherein ñ is a real number in the range of from 5 to 1500, such as from 5 to 800, for example from 5 to 600, such as from 5 to 400, for example from 5 to 300, for example from 5 to 200, such as from 5 to 100, for example from 5 to 90, such as from 5 to 80, for example from 5 to 70, such as from 5 to 60, for example from 5 to 50, such as from 5 to 45, for example from 5 to 40, such as from 5 to 30, for example from 5 to 25, such as from 10 to 25, for example from 10 to 20, such as from 10 to 15, for example from 15 to 20, such as from 11 to 19, for example from 12 to 18, such as from 13 to 17, for example from 10 to 12, such as from 12 to 14, for example from 14 to 16, such as from 16 to 18, for example from 18 to 20.

20. The polymer matrix according to claim 19, wherein the real number ñ is in the range of from 5 to 50.

21. The polymer matrix according to any of claims 19 and 20, wherein ã is a real number in the range of from 1 to 49, for example from 1 to 25, such as from 25 to 49, for example from 10 to 40, such as from 15 to 35, for example from 1 to 10, such as from 10 to 20, for example from 20 to 30, such as from 30 to 40, for example from 40 to 49, such as from 1 to 5, for example from 5 to 10, such as from 10 to 15, for example from 15 to 20, such as from 20 to 25, for example from 25 to 30, such as from 35 to 40, for example from 40 to 45, such as from 45 to 49.

22. The polymer matrix according to any of claims 19 and 20, wherein ã is 0.

23. The polymer matrix according to claim 21, wherein õ is 0.

24. The polymer matrix according to any of claims 19 and 20, wherein õ is a real number in the range of from 1 to 49, for example from 1 to 25, such as from 25 to 49, for example from 10 to 40, such as from 15 to 35, for example from 1 to 10, such as from 10 to 20, for example from 20 to 30, such as from 30 to 40, for example from 40 to 49, such as from 1 to 5, for example from 5 to 10, such as from 10 to 15, for example from 15 to 20, such as from 20 to 25, for example from 25 to 30, such as from 35 to 40, for example from 40 to 45, such as from 45 to 49.

25. The polymer matrix according to any of claims 19 and 20, wherein õ is 0.

26. The polymer matrix according to claim 24, wherein ã is 0.

27. The polymer matrix according to any of claims 19 and 20,

wherein ã is a real number in the range of from 0 to 49, for example from 1 to 25, such as from 25 to 49, for example from 10 to 40, such as from 15 to 35, for example from 0 to 10, such as from 10 to 20, for example from 20 to 30, such as from 30 to 40, for example from 40 to 49, such as from 0 to 5, for example from

5 to 10, such as from 10 to 15, for example from 15 to 20, such as from 20 to 25, for example from 25 to 30, such as from 35 to 40, for example from 40 to 45, such as from 45 to 49, and

wherein õ, independently of the value or range of ã, is a real number in the range of from 0 to 49, for example from 1 to 25, such as from 25 to 49, for example from 10 to 40, such as from 15 to 35, for example from 0 to 10, such as from 10 to 20, for example from 20 to 30, such as from 30 to 40, for example from 40 to 49, such as from 0 to 5, for example from 5 to 10, such as from 10 to 15, for example from 15 to 20, such as from 20 to 25, for example from 25 to 30, such as from 35 to 40, for example from 40 to 45, such as from 45 to 49.

28. The polymer matrix according to claim 27, wherein one of said intergers ã and õ is 0.

29. The polymer matrix according to claim 27, wherein ã is a real number in the range of from 0 to 10, and wherein õ is a real number in the range of from 0 to 10, such as from 10 to 20, for example from 20 to 30, such as from 30 to 40, for example from 40 to 49.

30. The polymer matrix according to claim 27, wherein ã is a real number in the range of from 10 to 20, and wherein õ is a real number in the range of from 0 to 10, such as from 10 to 20, for example from 20 to 30, such as from 30 to 39.

31. The polymer matrix according to claim 27, wherein ã is a real number in the range of from 20 to 30, and wherein õ is a real number in the range of from 0 to 10, such as from 10 to 20, for example from 20 to 29.

32. The polymer matrix according to claim 27, wherein ã is a real number in the range of from 30 to 40, and wherein õ is a real number in the range of from 0 to 10, such as from 10 to 19.

33. The polymer matrix according to claim 27, wherein ã is a real number in the range of from 40 to 49, and wherein õ is a real number in the range of from 0 to 9.

34. The polymer matrix according to any of the the previous claims, wherein said polymer matrix comprises at least about 30% (w/w) of a polyethyleneimine functionalized with at least one fragment comprising a vinyl group the polymerization of which is capable of generating the polymer matrix.

35. The polymer matrix according to claim 34, wherein said polymer matrix comprises from about 30 to 50 % (w/w) of a polyethyleneimine functionalized with at least one fragment comprising a vinyl group the polymerization of which is capable of generating the polymer matrix.

36. The polymer matrix according to claim 34, wherein said polymer matrix comprises from about 50 to 70 % (w/w) of a polyethyleneimine functionalized with at least one fragment comprising a vinyl group the polymerization of which is capable of generating the polymer matrix.

37. The polymer matrix according to claim 34, wherein said polymer matrix comprises from about 70 to 90 % (w/w) of a polyethyleneimine functionalized with at least one fragment comprising a vinyl group the polymerization of which is capable of generating the polymer matrix.

38. The polymer matrix according to claim 34, wherein said polymer matrix comprises more than 90 % (w/w) of a polyethyleneimine functionalized with at least one fragment comprising a vinyl group the polymerization of which is capable of generating the polymer matrix.

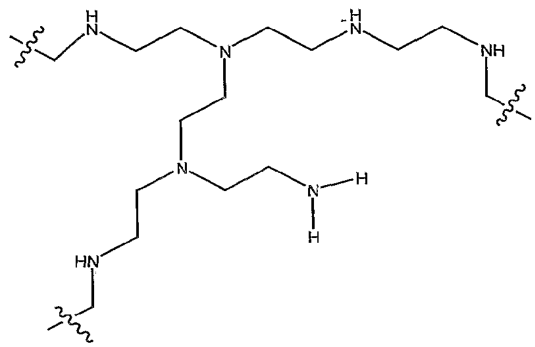
39. The polymer matrix according to any of the previous claims, wherein the number average molecular weight (M_n) of the polyethyleneimine is in the range of from 200 to 60000, such as from 200 to 45000, for example from 200 to 30000, such as from 200 to 25000, for example from 200 to 20000, such as from 200 to 15000, for example from 200 to 10000, such as from 200 to 8000, for example from 200 to 6000, such as from 200 to 5000, for example from 200 to 4500, such as from 200 to 4000, for example from 200 to 3500, such as from 200 to 3000, for example from 200 to 2500, such as from 200 to 2400, for example from 200 to 2300, such as from 200 to 2200, for example from 200 to 2100, such as from

200 to 2000, for example from 200 to 1900, such as from 200 to 1800, for example from 200 to 1700, such as from 200 to 1600, for example from 200 to 1500, such as from 200 to 1400, for example from 200 to 1300, such as from 200 to 1200, for example from 200 to 1100, such as from 200 to 1000, for example from 200 to 900, such as from 200 to 800, for example from 200 to 700, such as from 200 to 600, for example from 400 to 3000, such as from 400 to 2500, for example from 400 to 2000, such as from 400 to 1800, for example from 400 to 1600, such as from 400 to 1400, for example from 400 to 1200, such as from 400 to 1000, for example from 400 to 800, such as from 400 to 600, for example from 600 to 3000, such as from 600 to 2500, for example from 600 to 2000, such as from 600 to 1800, for example from 600 to 1600, such as from 600 to 1400, for example from 600 to 1200, such as from 600 to 1000, for example from 600 to 800, such as from 800 to 3000, for example from 800 to 2500, such as from 800 to 2000, for example from 800 to 1800, such as from 800 to 1600, for example from 800 to 1400, such as from 800 to 1200, for example from 800 to 1000, such as from 1000 to 3000, for example from 1000 to 2500, such as from 1000 to 2000, for example from 1000 to 1800, such as from 1000 to 1600, for example from 1000 to 1400, such as from 1000 to 1200.

40. The cross-linked and beaded polymer matrix according to claim 1 formed from a macromonomer comprising a polyethyleneimine and a polyfunctional alkylating agent, under inverse suspension or inverse emulsion polymerisation conditions.

41. The polymer matrix according to claim 40,

wherein the polyethyleneimine is optionally polydisperse and branched as illustrated by the formula (V)



and wherein the number of ethyleneimine units is from 5 to 50000, such as from 10 to 120, for example from 121 to 1200, such as from 1201 to 23000, for example from 23001 to 50000.

42. The beaded cross linked poly(aminoalkylene) matrix according to any of claims 40 and 41, wherein the polyfunctional alkylating agent is of the formula AXq,

wherein A is a saturated or unsaturated aliphatic and/or aromatic, or composed of both saturated and/or unsaturated aliphatic and aromatic fragments, and optionally containing heteroatoms such as silicon, nitrogen, phosphorous, oxygen, or sulphur;

wherein X is a reactive group; and

wherein q, is the number of reactive groups, such as 2, 3, 4, 5, or 6.

43. The beaded cross linked poly(aminoalkylene) matrix according to claim 42, wherein A is an aliphatic or alkylaryl group having 2 to 200 carbon atoms and optionally having 1 to 100 hetero atoms such as nitrogen, oxygen, or sulphur; preferably an aliphatic or alkylaryl group having 10 to 100 carbon atoms and optionally having 2 to 50 hetero atoms such as nitrogen, oxygen, or sulphur.

44. The beaded cross linked poly(aminoalkylene) matrix according to claim 42 wherein the cross linking unit A is selected from the group consisting of 1,2-ethylene, 1,3-propylene, 1,4-butylene, 1,4-butenylene, 1,5-pentylene, 1,6-hexylene, *o*-xylylene, *p*-xylylene, oxydiethyl, tri(ethylene oxide)diyl, tetra(ethylene oxide)diyl, penta(ethylene oxide)diyl, hexa(ethylene oxide)diyl,

hepta(ethylene oxide)diyl, octa(ethylene oxide), nona(ethylene oxide)diyl, deca(ethylene oxide)diyl, and a polydisperse poly(ethylene oxide)diyl, such as (ethylene oxide)$_{10}$diyl, polydisperse (ethylene oxide)$_{15}$diyl, polydisperse (ethylene oxide)$_{20}$diyl, polydisperse (ethylene oxide)$_{25}$diyl, polydisperse (ethylene oxide)$_{30}$diyl, polydisperse (ethylene oxide)$_{40}$diyl, and polydisperse (ethylene oxide)$_{45}$diyl, or comprises one ore more members of above defined group, including any combination of said group members.

45. The beaded cross linked poly(aminoalkylene) matrix according to any of claims 42 to 44, wherein X is a reactive group selected from

    a) S_N2 leaving groups
    b) Michael acceptors
    c) isocyanates
    d) carbonyl groups susceptible to reductive amination, with the option that the cross-linking step is followed by reduction of the imine to the amine, and
    e) N-(hydroxyalkyl) groups.

46. The beaded cross linked poly(aminoalkylene) matrix according to claim 45, wherein the reactive group X is selected from chloride, bromide, iodide, methanesulfonate, trifluoromethanesulfonate, p-toluenesulfonate, and epoxide.

47. The beaded cross linked poly(aminoalkylene) matrix according to claim 45, wherein the reactive group X is selected from acrylate, methacrylate, ethacrylate and acrylamido.

48. The beaded cross linked poly(aminoalkylene) matrix according to claim 45, wherein X is selected from alkyl isocyanate and aryl isocyanate.

49. The beaded cross linked poly(aminoalkylene) matrix according to claim 45, wherein X is selected from aldehydes and ketones susceptible to reductive ami

nation, with the proviso that the cross-linking step is followed by reduction of the imine to the amine.

50. The beaded cross linked poly(aminoalkylene) matrix according to claim 45, wherein X is a N-(hydroxymethyl) group.

51. The beaded cross linked poly(aminoalkylene) matrix according to claim 49, wherein the reducing agent comprises a borohydride, such as sodium borohydride or sodium cyanoborohydride, or an aluminium hydride, such as lithium aluminiumhydride, or sodium bis(2-methoxyethoxy)aluminiumhydride.

52. The beaded cross linked poly(aminoalkylene) matrix according to any of claims 42 to 51, wherein the cross linking molecule AXq is selected from ethylene dibromide, propylene dibromide, butylene dibromide, xylylene dibromide, ethylene glycol ditosylate, diethylene glycol dichloride, triethyleneglycol dichloride, polyethylene glycol dichloride, epichlorohydrine, ethylene glycol diglycidyl ether, diethylene glycol diglycidyl ether, triethylene glycol diglycidyl ether, polydisperse polyethylene glycol diglycidyl ether such as (ethylene oxide)$_{10}$, diglycidyl ether, (ethylene oxide)$_{15}$, diglycidyl ether (ethylene oxide)$_{20}$, diglycidyl ether, ethoxylated trimethylolpropane triglycidyl ether, and ethoxylated dipentaerythritol hexaglycidyl ether.

53. The beaded cross linked poly(aminoalkylene) matrix according to any of claims 42 to 51, wherein the cross linking molecule AXq is selected from ethylene glycol diacrylate, diethyleneglycol diacrylate, polyethylene glycol diacylate, polyethyleneglycol dimethacrylate, ethoxylated trimethylolpropane triacrylate, ethoxylated dipentaerythritol hexaacrylate, and Jeffamine diacrylate.

54. The beaded cross linked poly(aminoalkylene) matrix according to any of claims 42 to 51, wherein the cross linking molecule AXq is selected from 1,6-hexane diisocyanate, isophorone diisocyanate, toluene diisocyanate, and 1,4-phenylene diisocyanate.

55. The beaded cross linked poly(aminoalkylene) matrix according to any of claims 42 to 51, wherein the cross linking molecule AXq is selected from formaldehyde, glyoxal, succinaldehyde, glutaraldehyde, 1,4-diformylbenzene, 1,4-diacetylbenzene and polyethylene glycol 1,ω-bis(formylmethyl) ether, with the option that the cross-linking step is followed by reduction of the imine to the amine.

56. The beaded cross linked poly(aminoalkylene) matrix according to any of claims 42 to 51, wherein the cross linking molecule AXq is selected from N,N'-bis(hydroxymethyl)urea and a hydroxymethyl derivative of melamine, such as hexamethylolmelamine.

57. A beaded, cross-linked polymer comprising a matrix according to any of claims 1 to 56, preferably formed by polymerisation of droplets in an inert phase, such as unreactive oil, for example silicon oil, and preferably having an average diameter in the range of from 0.1 μ to 1000 μ.

58. The beaded, cross-linked polymer matrix according to claim 57, formed by bulk polymerisation.

59. The beaded, cross-linked polymer matrix according to claim 57, formed by inverse suspension polymerisation.

60. The beaded, cross-linked polymer matrix according to claim 57, formed by spray polymerisation.

61. The polymer matrix according to any of the previous claims, wherein the amine group loading capacity is in the range of from 0.1 to about 23 mmol/gram, for example from 0.1 to 20 mmol/gram, such as from 0.1 to 15 mmol/gram, for example from 0.1 to 10 mmol/gram, such as from 0.1 to 8 mmol/gram, for example from 0.1 to 6 mmol/gram, such as from 0.1 to 5 mmol/gram, for example from 0.1 to 4 mmol/gram, such as from 0.1 to 3 mmol/gram, for example from 0.1 to 2 mmol/gram, such as from 0.2 to 20 mmol/gram, for example from 0.4 to 20

mmol/gram, such as from 0.6 to 20 mmol/gram, for example from 0.8 to 20 mmol/gram, such as from 1.0 to 20 mmol/gram, for example from 2.0 to 20 mmol/gram, such as from 4.0 to 20 mmol/gram, for example from 6.0 to 20 mmol/gram, such as from 8.0 to 20 mmol/gram, for example from 10 to 20 mmol/gram, such as from 12 to 20 mmol/gram, for example from 14 to 20 mmol/gram, such as from 16 to 20 mmol/gram, for example from 18 to 20 mmol/gram, such as from 0.1 to 0.5 mmol/gram, for example from 0.5 to 1.0 mmol/gram, such as from 1.0 to 2.0 mmol/gram, for example from 2.0 to 4.0 mmol/gram, such as from 4.0 to 6.0 mmol/gram, for example from 6.0 to 8.0 mmol/gram, such as from 8.0 to 10 mmol/gram, such as from 10 to 12 mmol/gram, for example from 12 to 14 mmol/gram, such as from 14 to 16 mmol/gram, for example from 16 to 18 mmol/gram.

62. The polymer matrix according to any of the previous claims, wherein the swelling volume of the matrix in an aqueous liquid, including water, is in the range of from 1 ml/gram to preferably less than 32 ml/gram, such as from 1 ml/gram to 24 ml/gram, for example from 1 ml/gram to 20 ml/gram, such as from 1 ml/gram to 18 ml/gram, for example from 1 ml/gram to 16 ml/gram, such as from 1 ml/gram to 14 ml/gram, for example from 1 ml/gram to 12 ml/gram, such as from 1 ml/gram to 10 ml/gram, for example from 1 ml/gram to 9 ml/gram, such as from 1 ml/gram to 8 ml/gram, for example from 1 ml/gram to 7 ml/gram, such as from 1 ml/gram to 6 ml/gram, for example from 1 ml/gram to 5 ml/gram, such as from 1 ml/gram to 4 ml/gram, for example from 1 ml/gram to 3 ml/gram, such as from 1 ml/gram to 2 ml/gram, for example from 4 ml/gram to 20 ml/gram, such as from 4 ml/gram to 18 ml/gram, for example from 4 ml/gram to 16 ml/gram, such as from 4 ml/gram to 14 ml/gram, for example from 4 ml/gram to 12 ml/gram, such as from 4 ml/gram to 10 ml/gram, for example from 4 ml/gram to 8 ml/gram, such as from 4 ml/gram to 6 ml/gram, for example from 6 ml/gram to 20 ml/gram, such as from 6 ml/gram to 18 ml/gram, for example from 6 ml/gram to 16 ml/gram, such as from 6 ml/gram to 14 ml/gram, for example from 6 ml/gram to 12 ml/gram, such as from 6 ml/gram to 10 ml/gram, for example from 6 ml/gram to 8 ml/gram, such as from 8 ml/gram to 20 ml/gram, for example from 8 ml/gram to 16 ml/gram, such as from 8 ml/gram to 12 ml/gram, for example from 2 ml/gram to 4 ml/gram, such as from 8 ml/gram to 10 ml/gram, for example from 10 ml/gram to 12 ml/gram, such as from 12 ml/gram to 14 ml/gram,

for example from 14 ml/gram to 16 ml/gram, such as from 16 ml/gram to 18 ml/gram, for example from 18 ml/gram to 20 ml/gram.

63. The polymer matrix according to any of the previous claims, wherein the ratio R between i) the amine group loading capacity and ii) the swelling volume of the matrix in an aqueous liquid, including water, is in the range of from 0.1 to 20, such as from 0.1 to 18, for example from 0.1 to 16, such as from 0.1 to 14, for example from 0.1 to 12, such as from 0.1 to 10, for example from 0.1 to 9, such as from 0.1 to 8, for example from 0.1 to 7, such as from 0.1 to 6, for example from 0.1 to 5, such as from 0.1 to 4, for example from 0.1 to 3, such as from 0.1 to 2, for example from 0.1 to 1, such as from 0.1 to 0.5, for example from 2 to 20, such as from 2 to 18, for example from 2 to 16, such as from 2 to 14, for example from 2 to 12, such as from 2 to 10, for example from 2 to 8, such as from 2 to 6, for example from 2 to 4, such as from 1 to 10, for example from 10 to 20, such as from 1 to 4, for example from 4 to 8, such as from 8 to 12, for example from 12 to 16, such as from 16 to 20.

64. The polymer matrix accoding to any of the previous claims, wherein said matrix is beaded and preferably has a spherical form.

65. A method for generating the beaded and cross-linked polymer matrix according to any of claims 41 to 64, said method comprising the steps of:

b) providing a polyethyleneimine of formula V, wherein the number of ethyleneimine units is from 5 to 60000, such as from 10 to 120, for example from 121 to 1200, such as from 1201 to 23000, for example from 23001 to 50000,

c) providing and a cross-linking molecule AXq, wherein A is a saturated or unsaturated aliphatic and/or aromatic, or composed of both saturated and/or unsaturated aliphatic and aromatic fragments, and optionally containing heteroatoms such as silicon, nitrogen, phosphorous, oxygen, or sulphur; wherein X is a reactive group; and wherein q, is the number of reactive groups, such as 2, 3, 4, 5, or 6

d) reacting under beading conditions the polyethyleneimine provided in step a) with the the cross-linking molecule AXq provided in step b), and

e) obtaining a cross-linked and beaded polymer matrix according to any of claims 1 to 64.

66. The method of claim 65, wherein the polyethyleneimine of formula V is mixed with AXq in the presence of a surface active agent.

67. The method of any of claims 65 and 66 wherein a solvent is present.

68. The method of any of claims 65 to 67, wherein the reaction mixture is added with stirring or ultrasonification to a liquid not miscible with the reactive mixture, preferably in a predetermined specific ratio and at a temperature at which the bead formation and cross linking is fast.

69. The method of any of claims 65 to 68, wherein a nucleophilic catalyst or a basic catalyst is present.

70. The method of any of claims 66 to 69, wherein the surface active agent is added to the reactive phase and/or to the non-reactive phase.

71. The method of any of claims 65 to 70, wherein stoechiometry of the reactants is defined by the molar ratio of nitrogens of the polyethyleneimine of formula V to X of AXq (mol N/mol X) is 500 to 0.1.

72. The method of any of claims 65 to 70, wherein stoechiometry of the reactants is defined by the molar ratio of nitrogens of the polyethyleneimine of formula V to X of AXq (mol N/mol X) is 100 to 0.5.

73. The method of any of claims 65 to 70 wherein stoechiometry of the reactants is defined by the molar ratio of nitrogens of the polyethyleneimine of formula V to X of AXq (mol N/mol X) is 50 to 0.9.

74. The method of any of claims 65 to 73, wherein the reaction is run neat or in the presence of a solvent.

75. The method of any of claims 65 to 73, where the reaction is run in the presence of a solvent selected from water, methanol, ethanol, ethylene glycol, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidone, or acetonitrile.

76. The method of any of claims 65 to 75 where the concentration of the reaction solution is from 5 to 100%, such as from 10 to 80%, for example from 20 to 60%.

77. The method of any of claims 65 to 76 where the stirring frequency is from 1 to 2000 rpm, for example from 50 to1000 rpm, for example from 100 to 500 rpm, such as from 200 to 400 rpm.

78. The method of any of claims 68 to 77, wherein the non-miscible liquid is a petroleum fraction, an aliphatic oil, a natural fat or triglyceride, an aromatic solvent such as toluene or xylene, a halogenated solvent such as methylene chloride, chloroform, carbon tetrachloride, dichloroethane, trichloroethylene, chlorobenzene, a fluorinated solvent, or mixtures thereof.

79. The method of any of claims 68 to 78, wherein the ratio of the reactive phase and the nonmiscible liquid is from 2:1 to 1:100, such as from 4:5 to 1:75, for example from 1:2 to 1:30.

80. The method of claims 69 to 79, wherein the nucleophilic catalyst is a salt such as sodium bromide, sodium iodide, potassium iodide, or tetrabutylammonium bromide.

81. The method of any of claims 69 to 80, wherein the basic catalyst is an alkaline compound such sodium hydrogen carbonate, potassium carbonate, potassium hydroxide, or tetrabutylammonium hydroxide.

82. The method of any of claims 66 to 81, wherein the surface active agent is selected from the group consisting of negatively charged surface active agent such as sodium laurate, sodium lauryl sulfate, sodium laurylsulfonate, and sodium decylbenzenesulfonate.

83. The method of any of claims 66 to 81, wherein the surface active agent is selected from the group consisting of neutral surface active agent such as ethoxylated aliphatic alcohols, ethoxylated alkylphenols, alkylphenols, carbohydrate derived esters, e.g., sorbitan laurate, amphiphilic polymers such as copolymers of polyethylene glycol methacrylate and lauryl acrylate or trialkylsilylalkyl methacrylate or copolymers of ethylene oxide and propylene oxide, and homopolymers, such as polyvinyl acetate or completely or partially hydrolysed polyvinyl acetate.

84. The method of any of claims 66 to 81, wherein the surface active agent is selected from the group consisting of positively charged surface active agents such as hexadecyltrimethylammonium bromide, tetraheptylammoinum chloride and tetrabutylammonium bromide.

85. The method of any of claims 65 to 84, wherein the reaction temperature is from –20°C to 150°C, such as from 20°C to 100°C, for example from 40°C to 80°C.

86. Use of the polymer matrix according to any of claims 1 to 64 for a support for the synthesis of an organic molecule.

87. Use of the polymer matrix according to any of claims 1 to 64 for scavenging excess acyl compounds from a composition comprising a mixture of molecular entities.

88. The use of claim 87, wherein the mixture of molecular entities result from amine reactions and/or acylation reactions.

89. Use of the polymer matrix according to any of claims 1 to 64 for scavenging excess carbonyl compounds from a composition comprising a mixture of molecular entities.

90. The use of claim 89, wherein the mixture of molecular entities result from organometallic reagent addition reactions and/or carbonyl compound addition reactions.

91. Use of the polymer matrix according to any of claims 1 to 64 for solid phase enzyme reactions.

92. Use of the polymer matrix according to any of claims 1 to 64 for a support for the synthesis of a peptide, a protein, a DNA, and a RNA.

93. Use of the polymer matrix according to any of claims 1 to 64 for protein immobilisation.

94. Use of the polymer matrix for chromatographic separation or purification.

95. The use of claim 94, wherein the chromatographic separation or purification comprises at least one step employing affinity purification.

96. Use of the polymer matrix for a support for combinatorial chemistry.

97. Use of a partially acryloylated polyethylenimine in the preparation of an optionally beaded, cross-linked polymer matrix according to any of claims 1 to 64.

98. The use of claim 97, wherein the preparation comprises the step of inverse suspension polymerization.

99. Use of the polymer matrix according to any of claims 1 to 64 for scavenging metals ions.

100. The use of claim 99, wherein the metals are bi-products in organometallic reactions, metal ions in effluent water, such as sewage water, or metal ions from ore or metal scrap.

101. The use of claim 99, wherein the metal is selected from metals in periods 4 and 5 of the periodic system, including the Lanthanides.

102. The use of claim 99, wherein the metal is selected from metals in period period 6 of the periodic system, including the Actinides.

103. The use of claim 99, wherein the metal is palladium.

104. The use of claim 99, wherein the metal is cupper.

105. A composition comprising a plurality of beaded and cross-linked polymer matrices according to any of claims 1 to 64.

106. The composition according to claim 105, wherein the average diameter is in the range of from 0.1 μ to preferably less than 1000 μ.

107. A functional surface comprising a polymer matrix according to any of claims 1 to 64, and attached thereto at least one functional moiety.

108. The functional surface according to claim 107, wherein the functional moiety is a bioactive species preferably selected from RNA, DNA, a peptide, and an amino acid residue.

109. The functional surface according to claim 107, wherein said surface is solid.

110. The functional surface according to claim 107, wherein said surface further comprises a linker residue.

111. The functional surface according to claim 107, said surface being obtained by converting at least some of the amino groups of the polymer matrix according to any of claims 1 to 64 after polymerisation and beading, thereby generating a functional surface of the structure

(polymer matrix)–NR^1R^2,

or a functional surface of the structure

(polymer matrix)–NR^3–(polymer matrix),

wherein R^1, R^2 and R^3 are independently H, or an organic group formed by reaction of the amino groups of the polymer matrix according to any of claims 1 to 64 with an alkylating agent or an acylating agent.

112. The functional surface according to claim 111, wherein the alkylating agent is selected from an alkyl halide or a substituted alkyl halide.

113. The functional surface according to claim 111, wherein the alkylating agent is selected from an alkyl sulphonate or a substituted alkyl sulphonate.

114. The functional surface according to claim 111, wherein the alkylating agent is an epoxide.

115. The functional surface according to claim 111, wherein the alkylating agent is selected from Michael electrophiles.

116. The functional surface according to claim 111, wherein the alkylation agent is selected from methyl iodide, ethyl iodide, propyl bromide, butyl bromide, chloroacetic acid, benzyl chloride, benzyl bromide, methylbenzyl bromide, methoxybenzyl bromide, and nitrobenzyl bromide.

117. The functional surface according to claim 111, wherein the alkylating agent is selected from Methyl methanesulphonate, methyl trifluoromethanesulphonate and methyl p-toluenesulphonate.

118. The functional surface according to claim 111, wherein the alkylating agent is selected from ethylene oxide, propylene oxide and a glycidol derivative.

119. The functional surface according to claim 111, wherein the alkylating agent is selected from methyl acrylate and ethyl acrylat

120. The functional surface according to claim 111, wherein the acylating agent is selected from a carboxylic acid, an activated carboxylic acid, a carbonic acid derivative and a heteroallene

121. The functional surface according to claim 111, wherein the acylating agent is selected from formic acid, acetic acid, propionic acid, benzoic acid, mercaptoacetic acid, 3-mercaptopropanoic acid, thiolactic acid, and protected

aminoacids, such as N-(fluorenyloxymethylcarbonyl)glycine or N-(benzyloxycarbonyl)alanine, or N-(*t*-butoxycarbonyl)phenylalanine, or derivatives thereof, optionally activated by condensing agents such as dicyclohexylcarbodiimide.

122. The functional surface according to claim 111, wherein the acylating agent is selected from acetic anhydride, acetyl chloride, ethyl acetate and benzoyl chloride.

123. The functional surface according to claim 111, wherein the acylating agent is selected from methyl chloroformate, *t*-butyl chloroformate, benzyl chloroformate and diphenyl carbonate.

124. The functional surface according to claim 111, wherein the acylating agent is selected from ethyl isocyanate, phenyl isocyanate, ethyl isothiocyanate and phenyl isothiocyanate.

125. A method for preparing the polymer matrix according to any of claims 1 to 64, optionally in beaded form, said method comprising the steps of

a) providing a macromonomer comprising a polyethyleneimine functionalized with at least one fragment comprising a vinyl group, and

b) polymerising the vinyl groups of said macromonomers using radical or ionic initiators to form the cross-linked polymer matrix.

126. The method of claim 125 comprising the further step of chemically reducing the amide functionalities and thereby generating a resin wherein the majority of the amide functionalities are reduced to secondary amine functionalities.

127. A method for preparing a functional surface according to any of claims 107 to 124, said method comprising the steps of

a) cross-linking a plurality of partially acryloylated polyethylenimines, and

b) contacting said functional surface comprising said cross-linked partially acryloylated polyethylenimines with at least one functional moiety.

128. Method for targeting a functional moiety attached to a functional surface, said method comprising the steps of

a) providing a functional surface according to any of claims 107 to 124, and

b) targeting said functional moiety with at least one targeting species having an affinity for said functional moiety.

129. Method for identifying and/or purifying a targeting species having an affinity for a functional moiety, said method comprising the steps of

a) providing a functional surface according to any of claims 62 to 65,

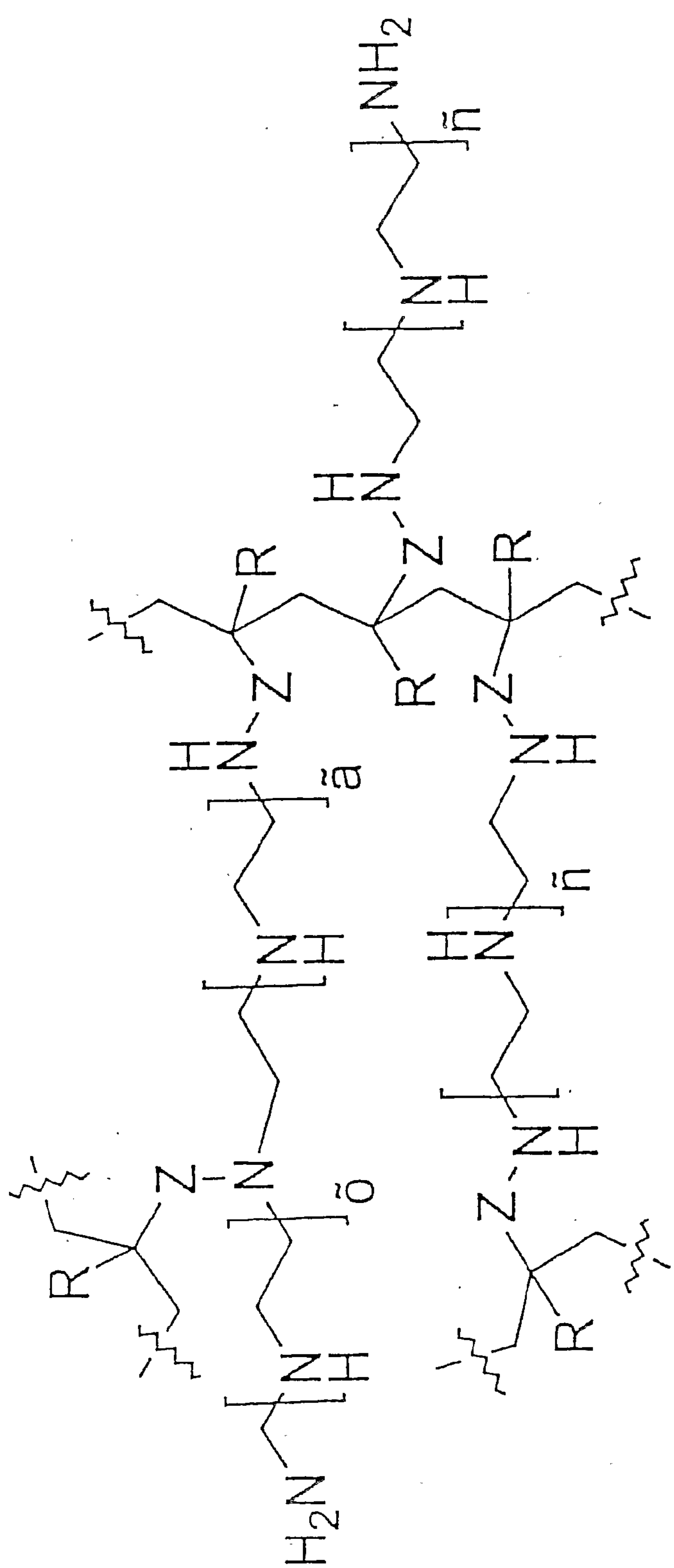
b) targeting said functional moiety with at least one targeting species having an affinity for said functional moiety, and

c) identifying and/or purifying the at least one targeting species having an affinity for said functional moiety.

130. Targeting species identified by the method of claim 70.

131. A method for therapy of a human or animal body, said method comprising the step of administering to said human or animal body a targeting species according to claim 130 in a pharmaceutical effective amount.

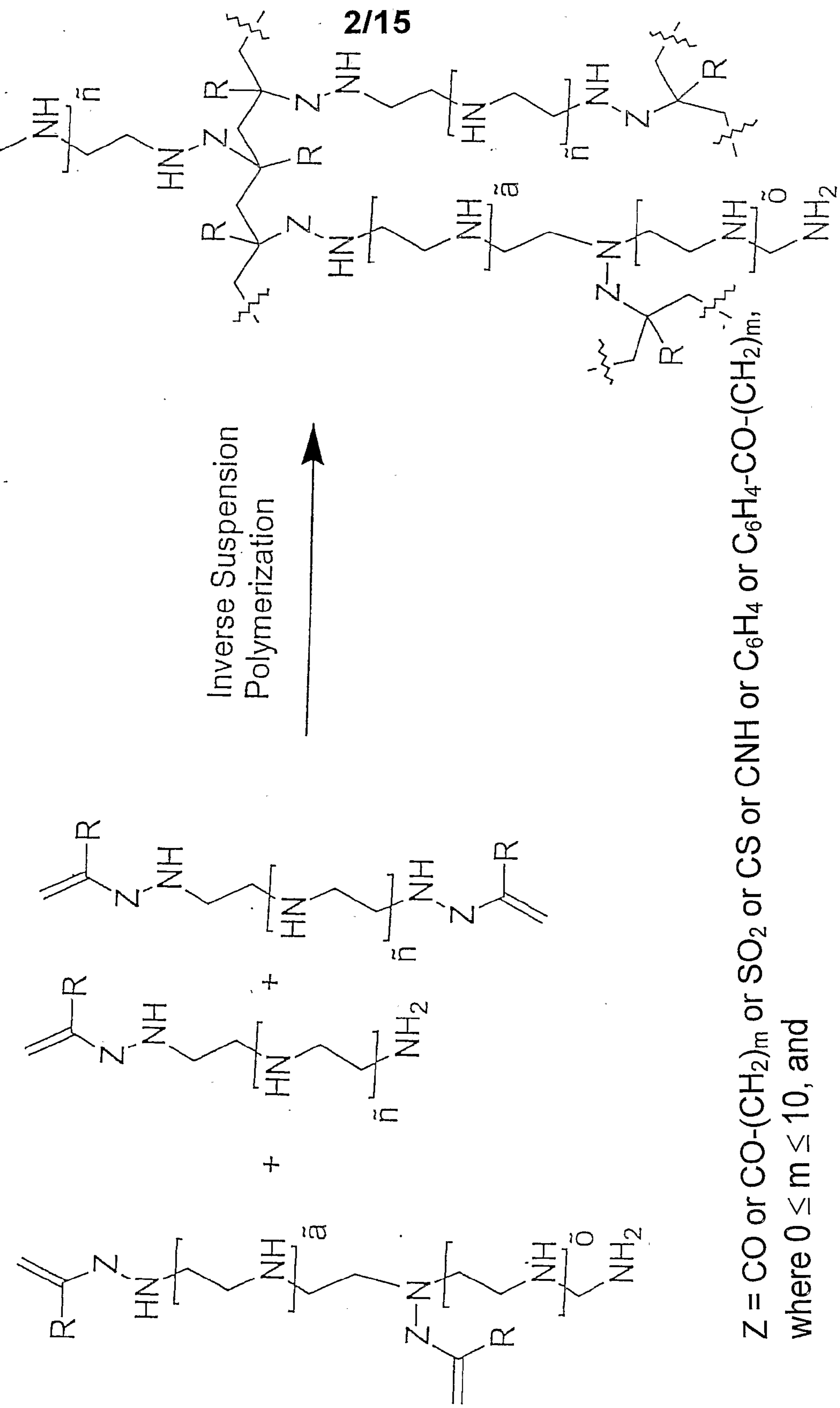
Fig. 1



Z = CO or CO-$(CH_2)_m$ or SO_2 or CS or CNH or C_6H_4 or C_6H_4-CO-$(CH_2)_m$, where $0 \leq m \leq 10$,
R = H or CH_3 or C_2H_5.

2/15

Fig. 2



Z = CO or CO-$(CH_2)_m$ or SO_2 or CS or CNH or C_6H_4 or C_6H_4-CO-$(CH_2)_m$, where $0 \leq m \leq 10$, and

R = H or CH_3 or C_2H_5.

Fig. 3

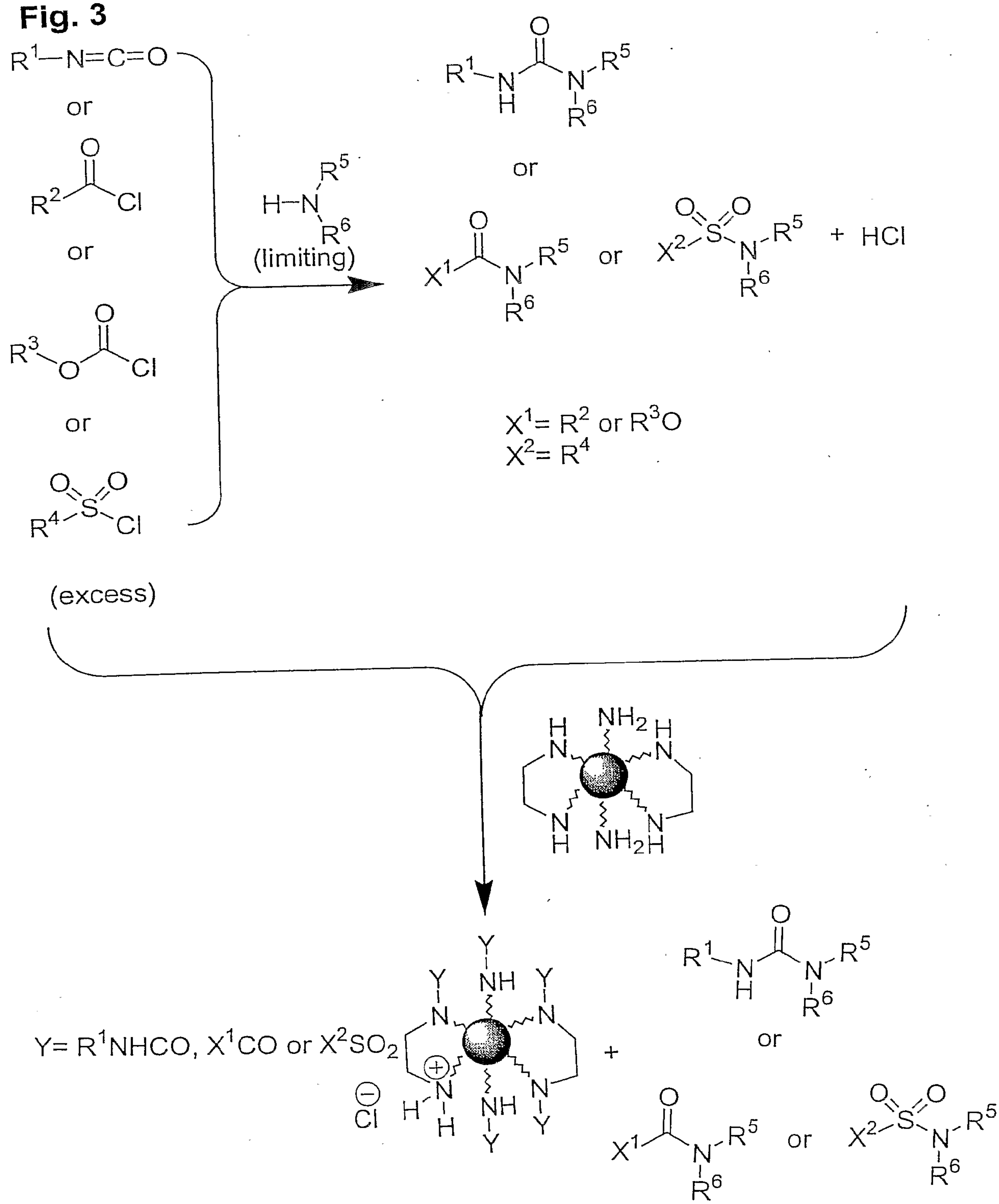

R1—N=C=O
or
R2 Cl O
or
R3 O Cl O
or
R4 S Cl O O
(excess)
H—N R5 R6
(limiting)
X1= R2 or R3O
X2= R4
+ HCl
NH2
Y= R1NHCO, X1CO or X2SO2
+
or

Fig. 4

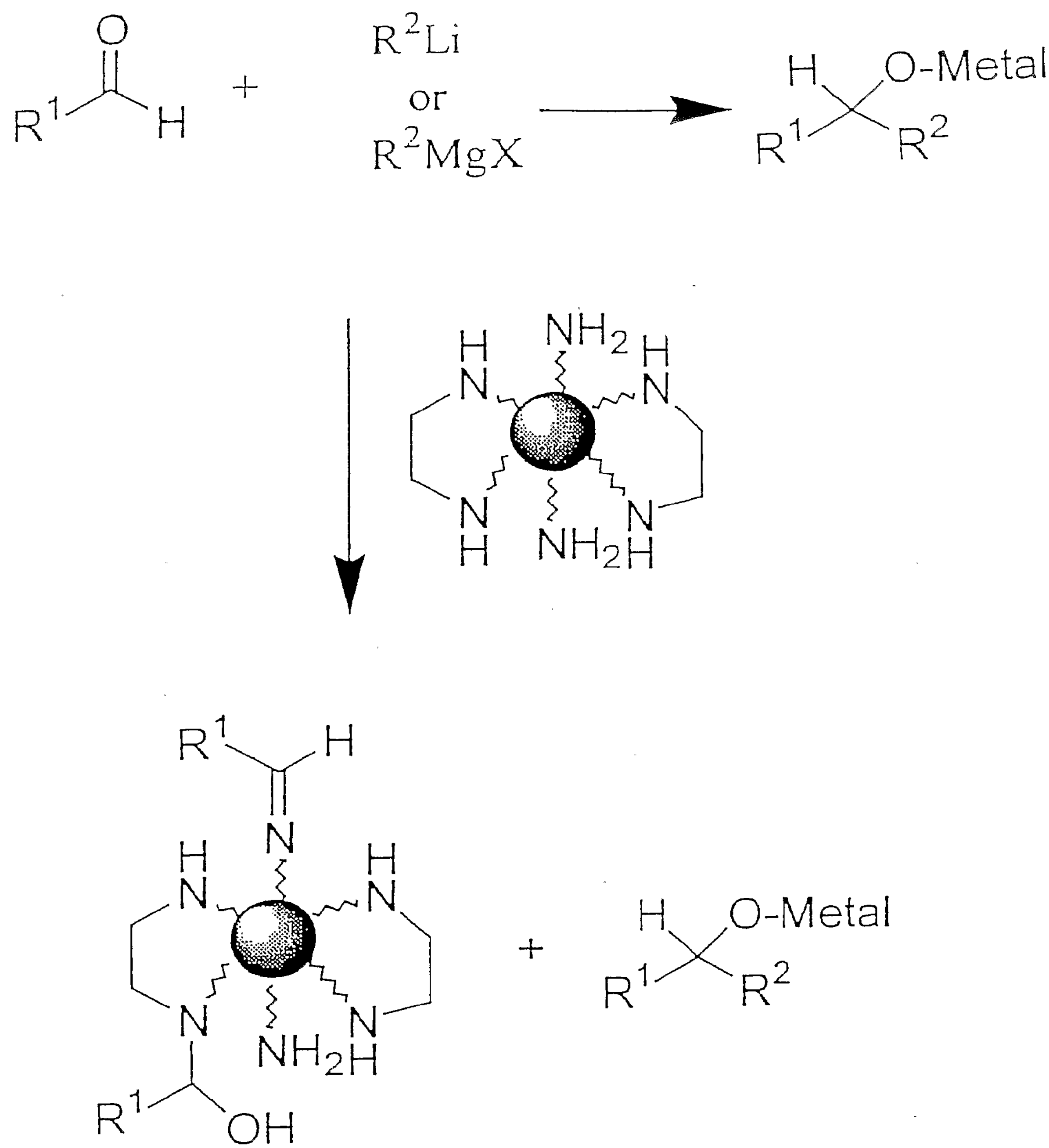

O
R^1
H
+
R^2Li
or
R^2MgX
H
O-Metal
R^1
R^2
H
N
NH_2
H
N
N
H
NH_2
N
H
R^1
H
N
H
N
H
N
N
NH_2
N
H
R^1
OH
+
H
O-Metal
R^1
R^2

Fig. 5

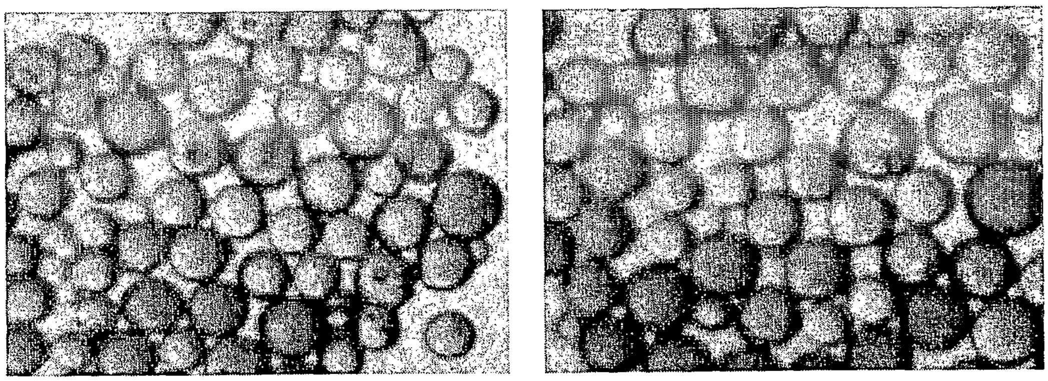
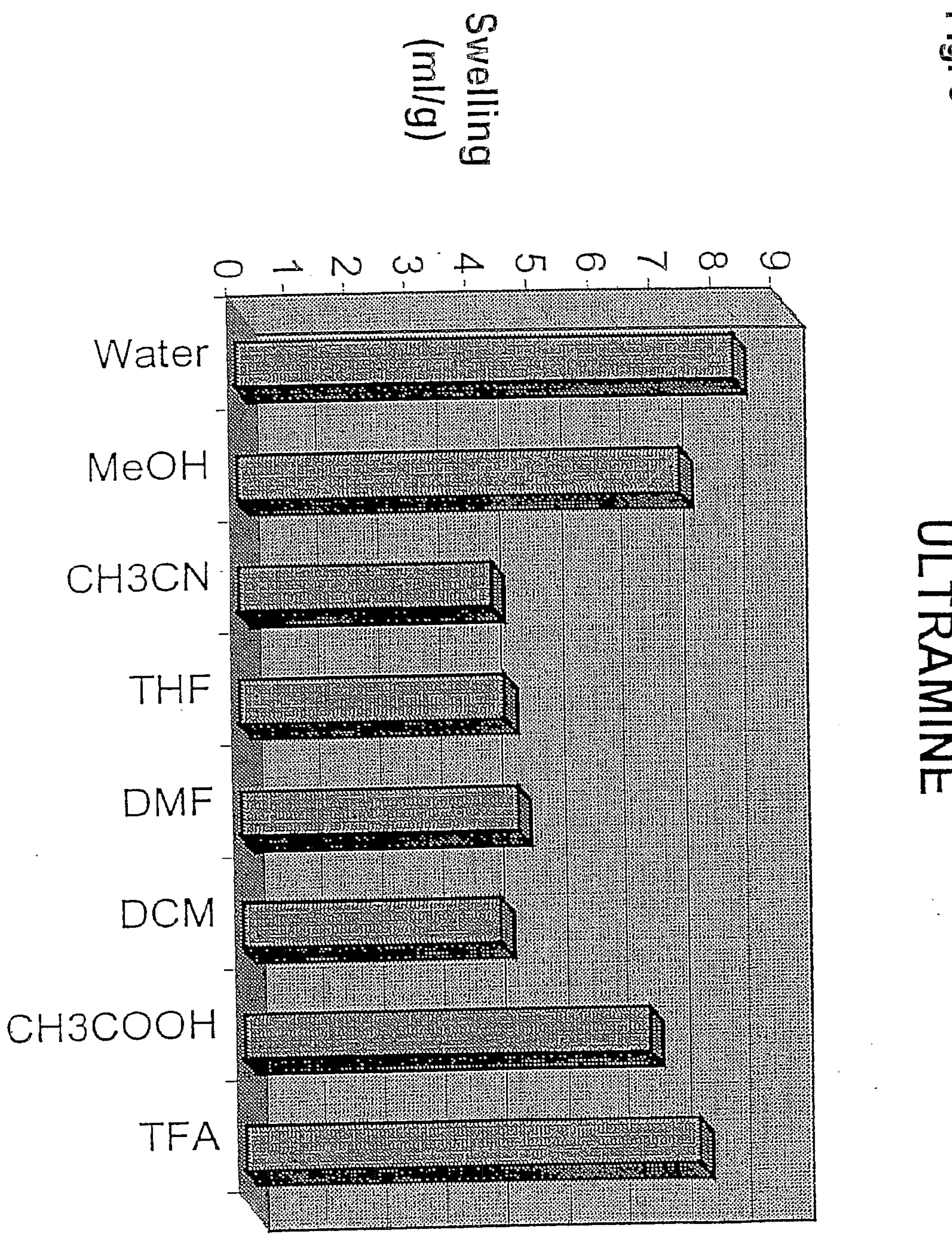


Fig. 6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Swelling
(ml/g)
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1
2
3
4
5
6
7
8
9
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MeOH
CH3CN
THF
DMF
DCM
CH3COOH
TFA

Fig. 7

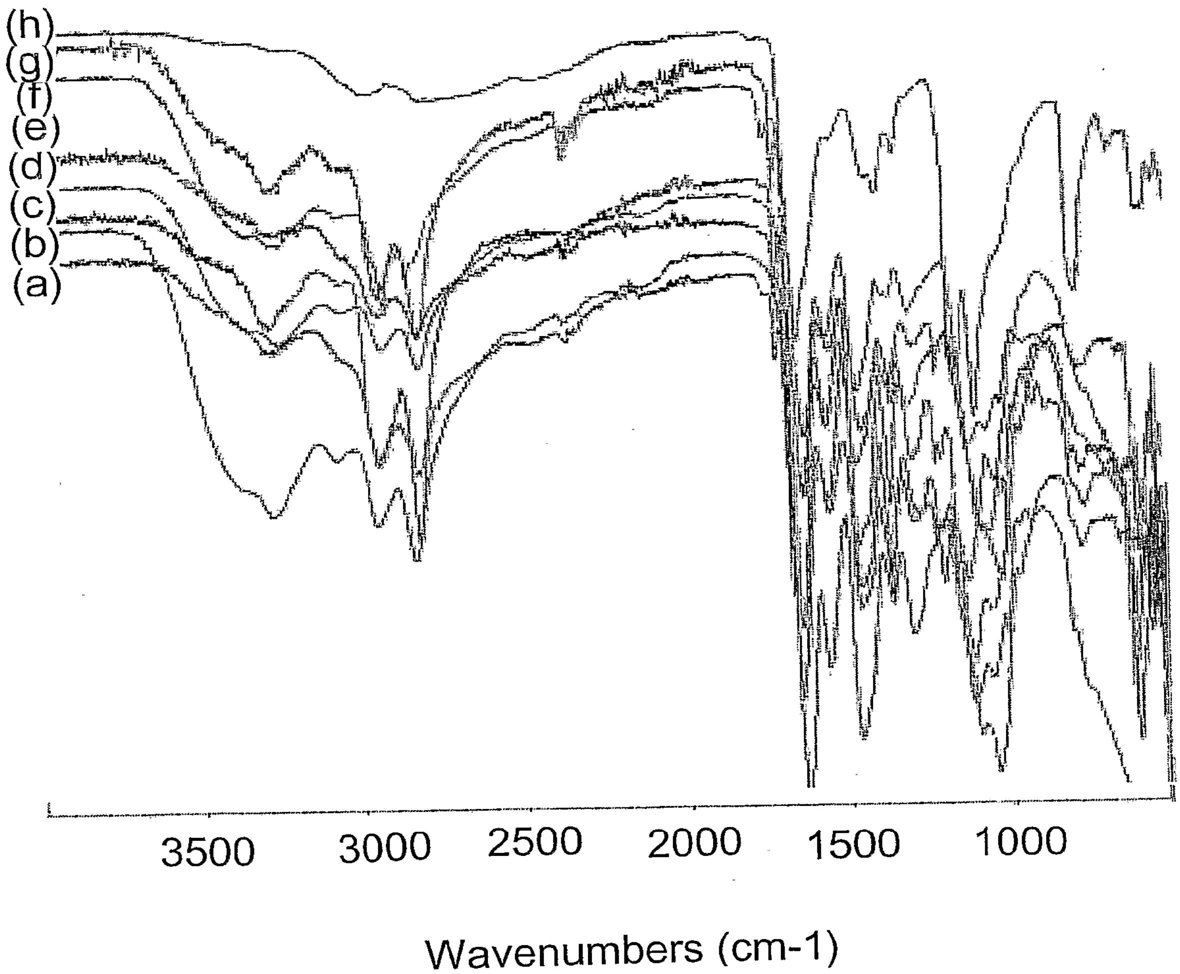


Fig. 8

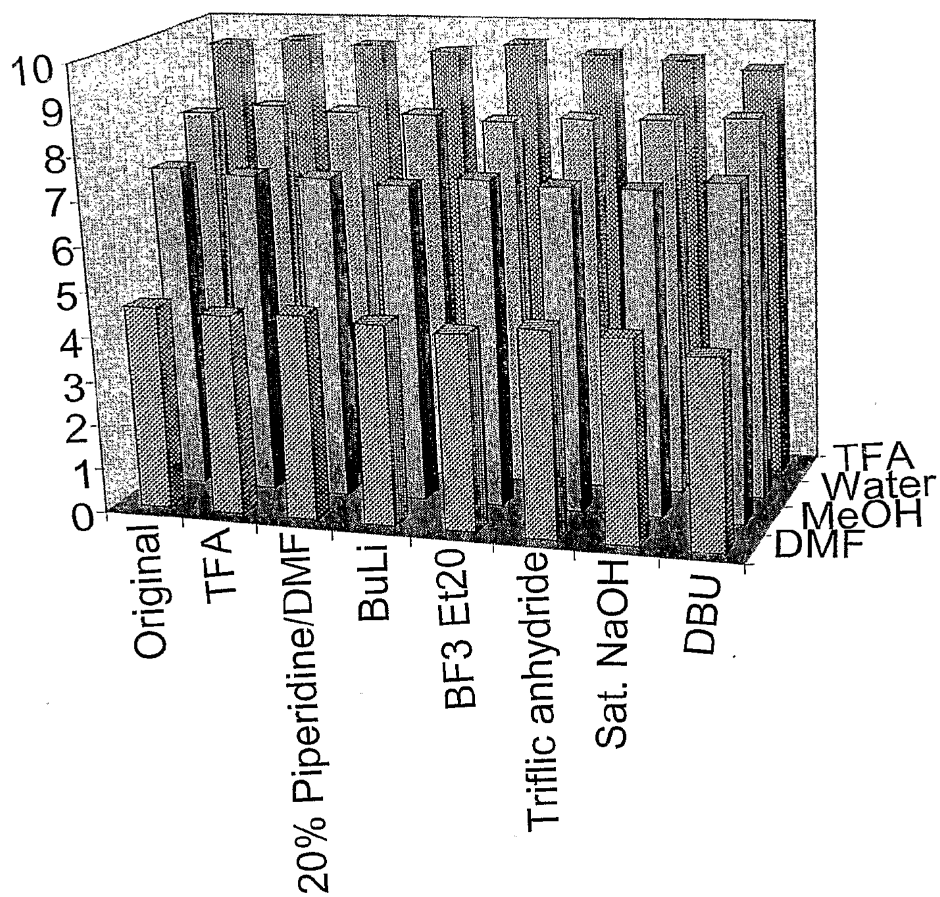

10
9
8
7
6
5
4
3
2
1
0
Original
TFA
20% Piperidine/DMF
BuLi
BF3 Et20
Triflic anhydride
Sat. NaOH
DBU
TFA
Water
MeOH
DMF

Fig. 9

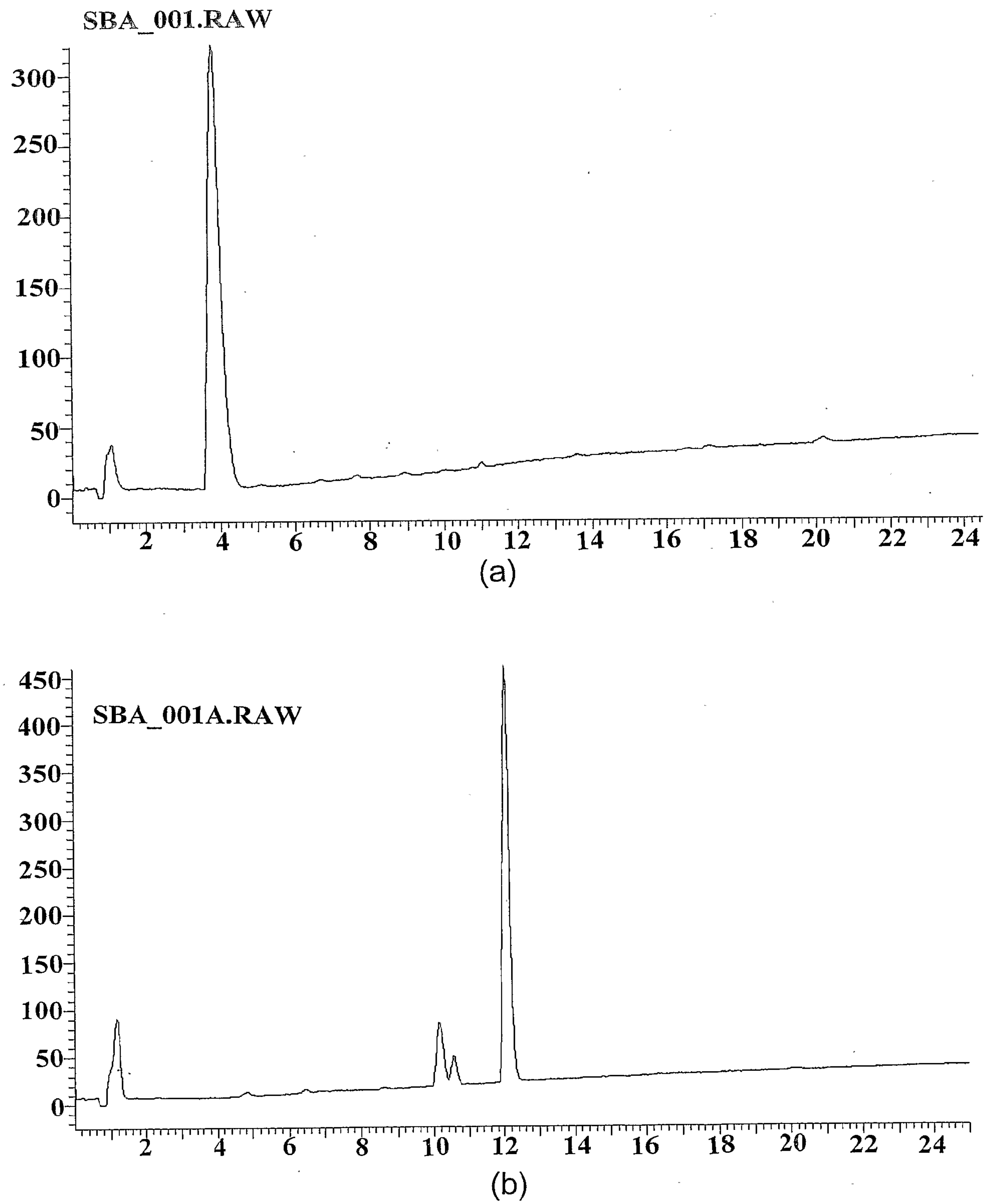
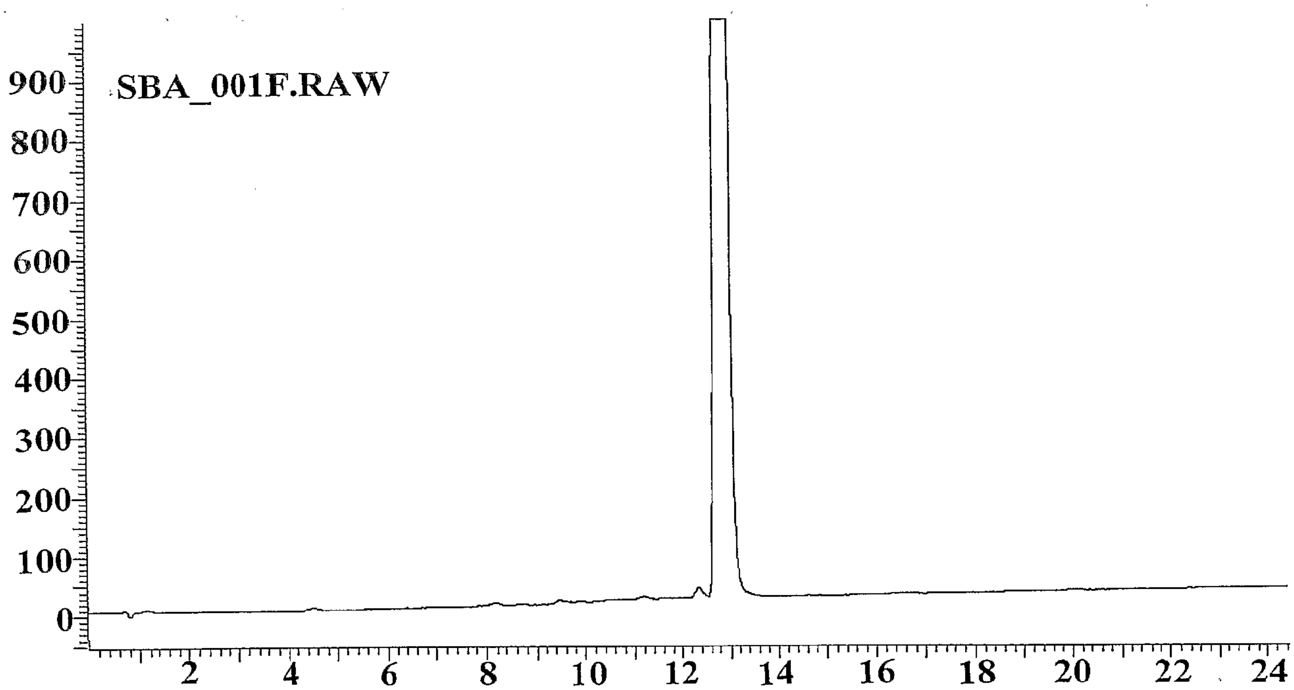
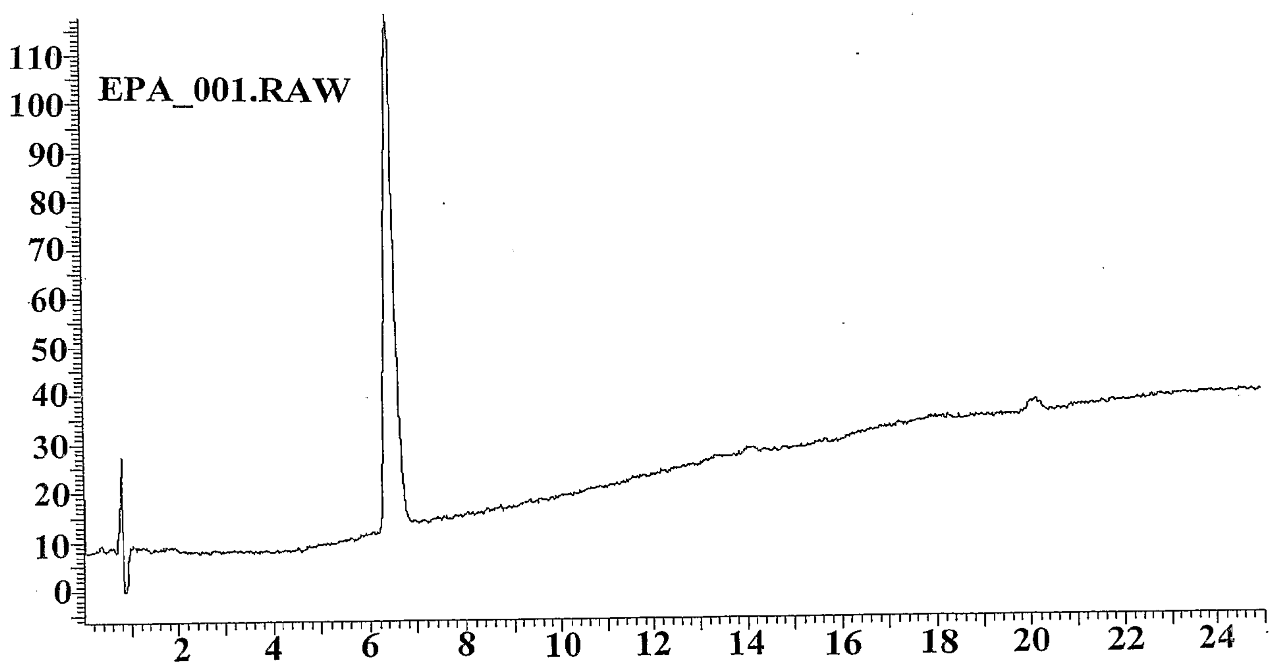

SBA_001.RAW
300
250
200
150
100
50
0
2 4 6 8 10 12 14 16 18 20 22 24
(a)
450
400
350
300
250
200
150
100
50
0
SBA_001A.RAW
2 4 6 8 10 12 14 16 18 20 22 24
(b)

Fig. 9 (continued)

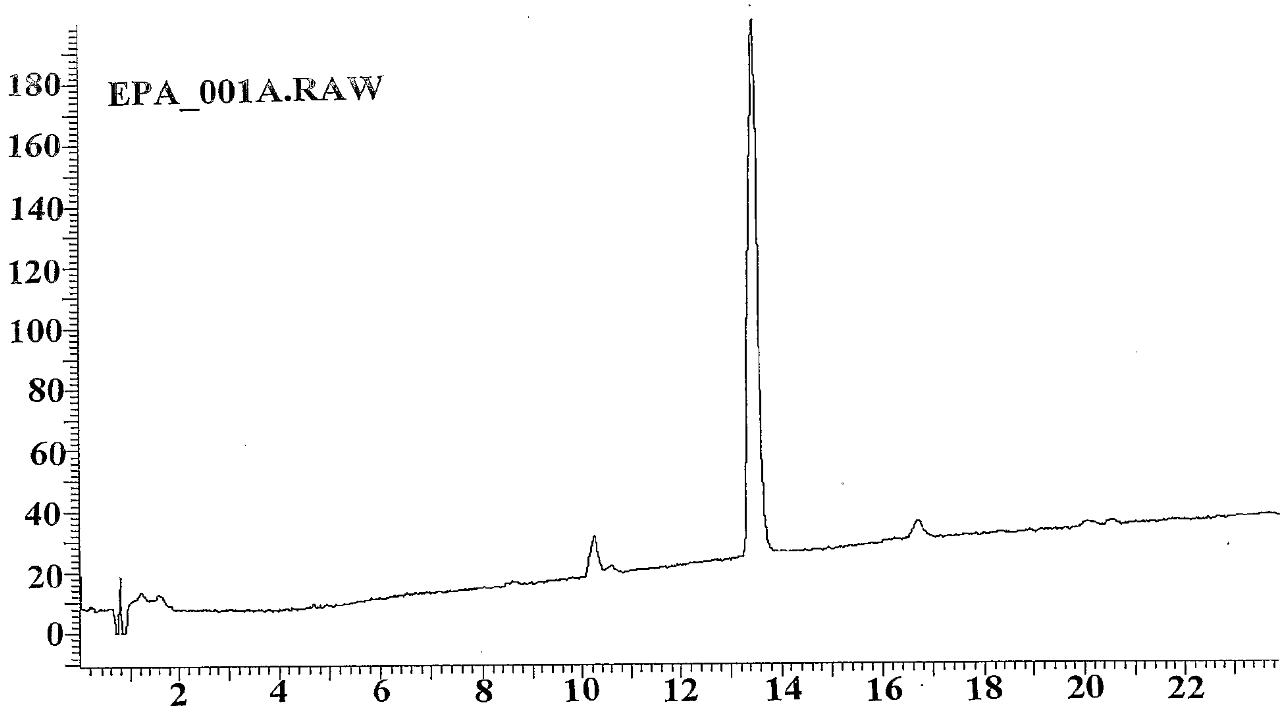


(c)

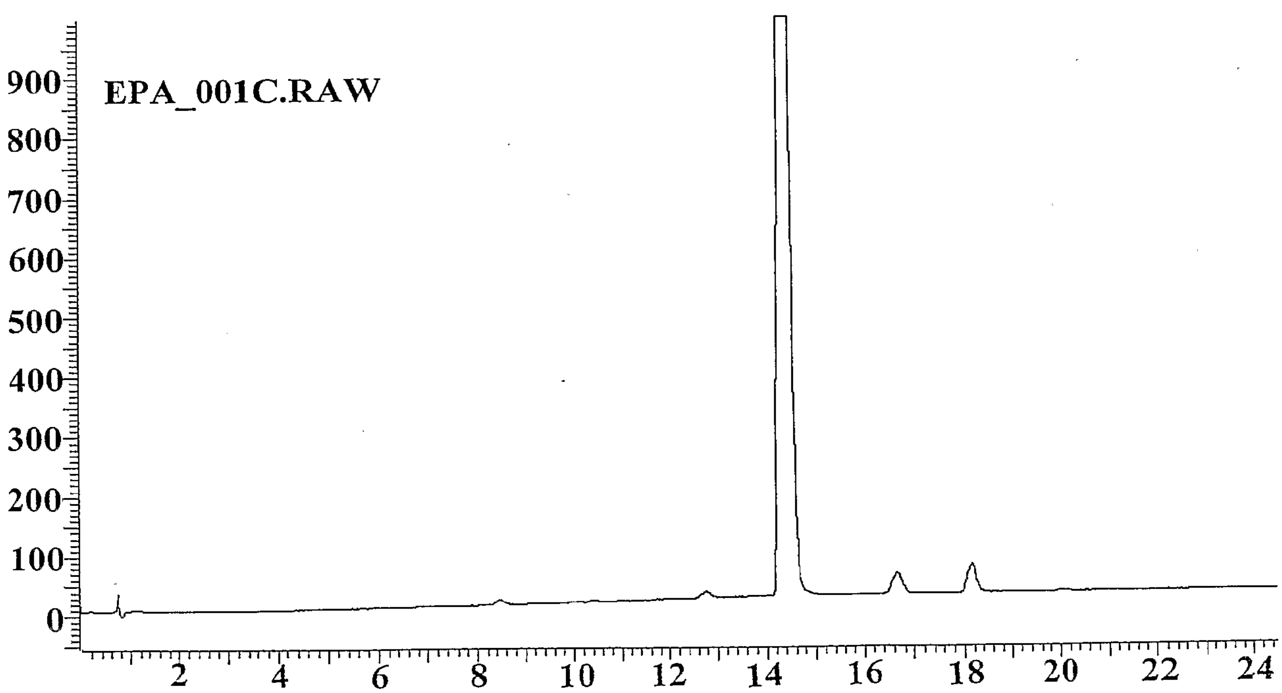


(d)

Fig. 9 (continued)

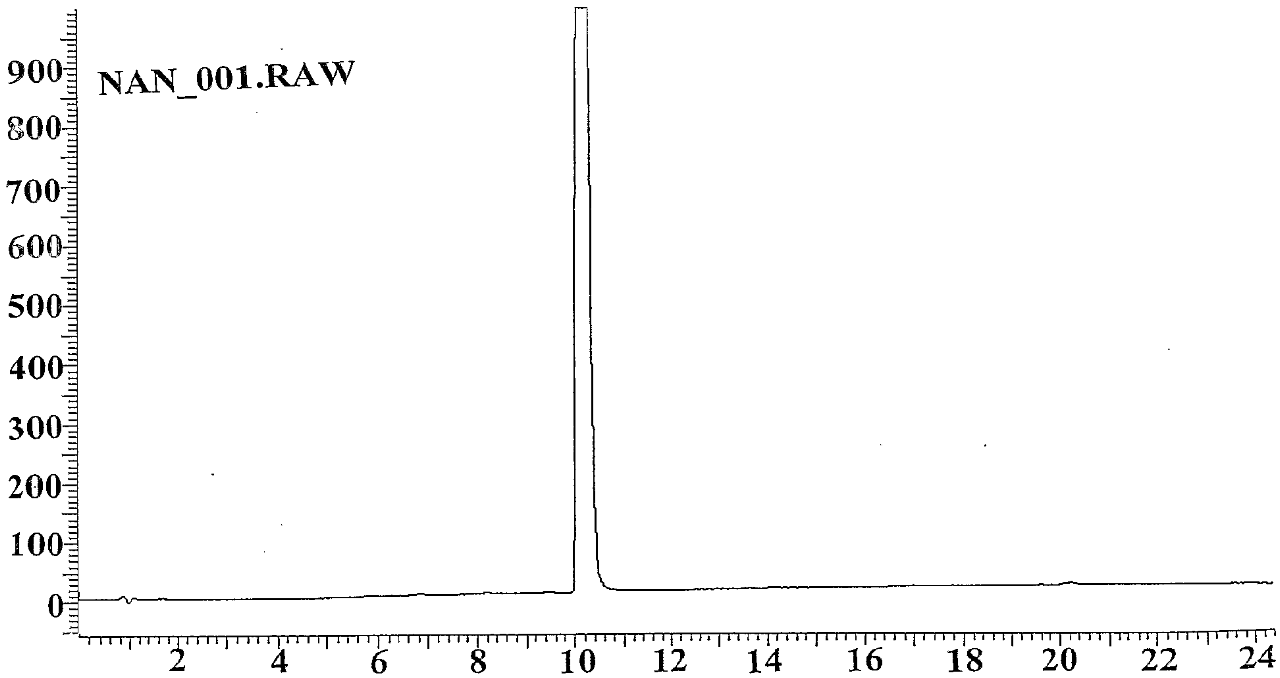


(e)

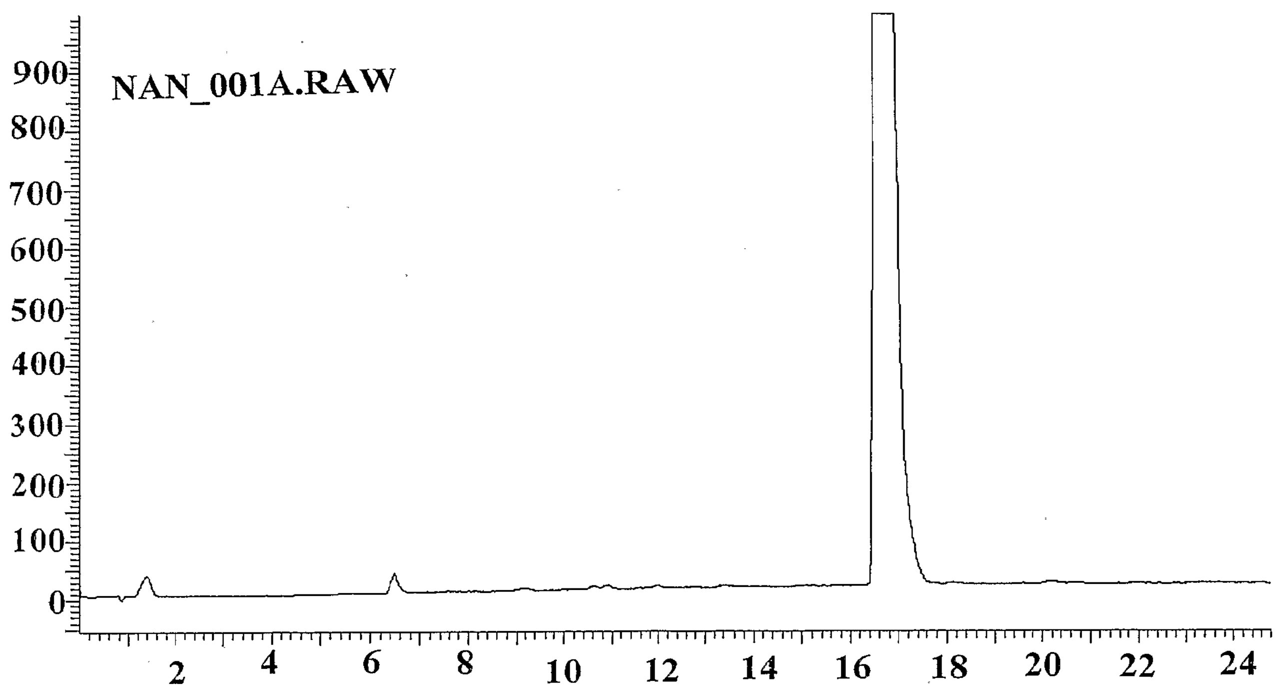


(f)

Fig. 9 (continued)

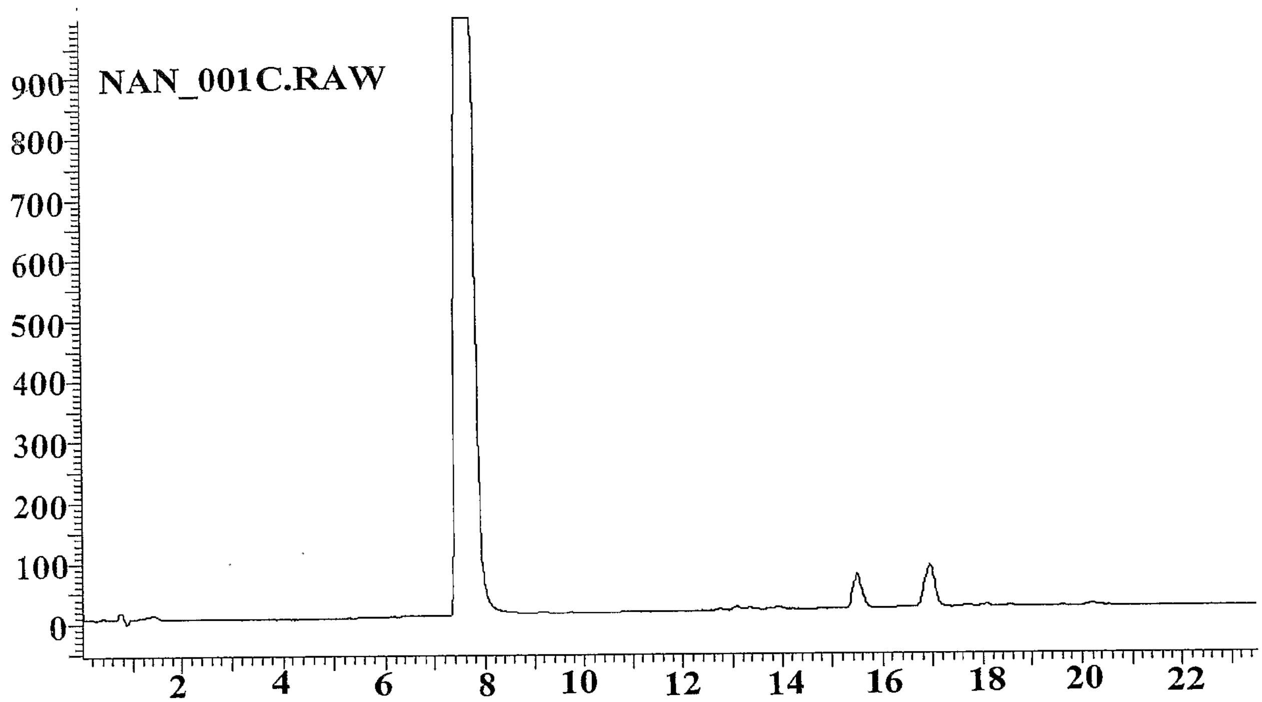


(g)

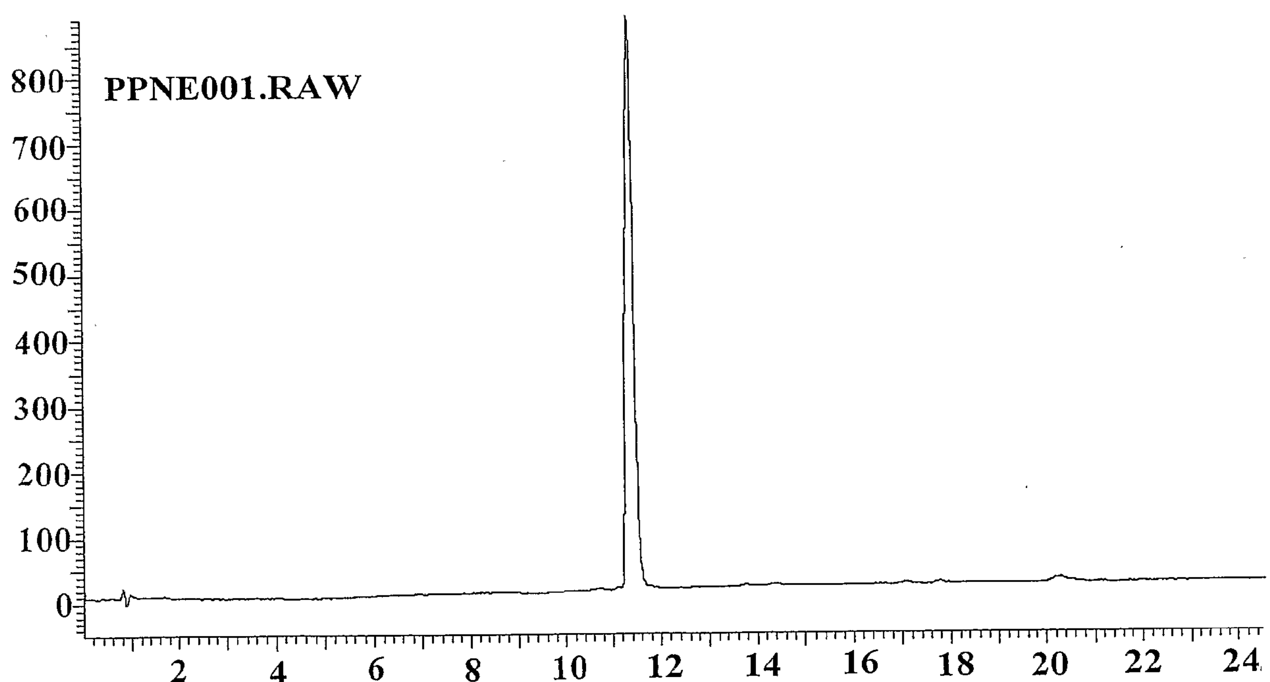


(h)

Fig. 9 (continued)

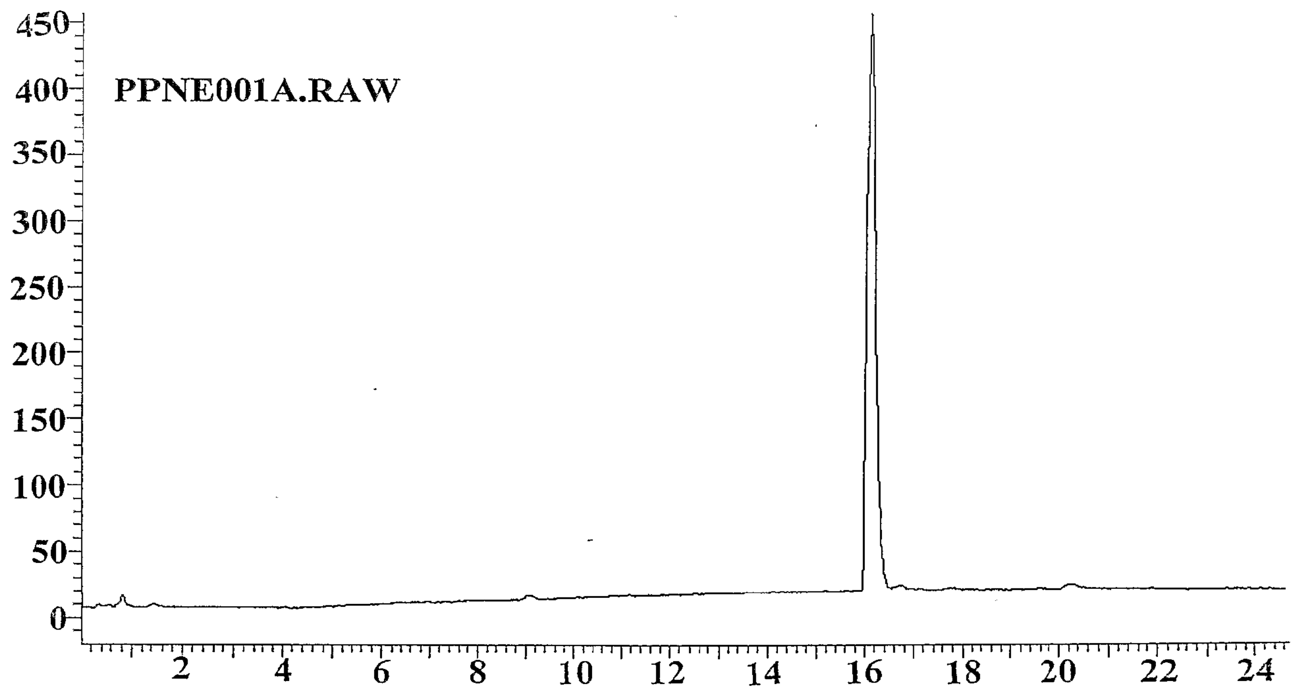


(i)

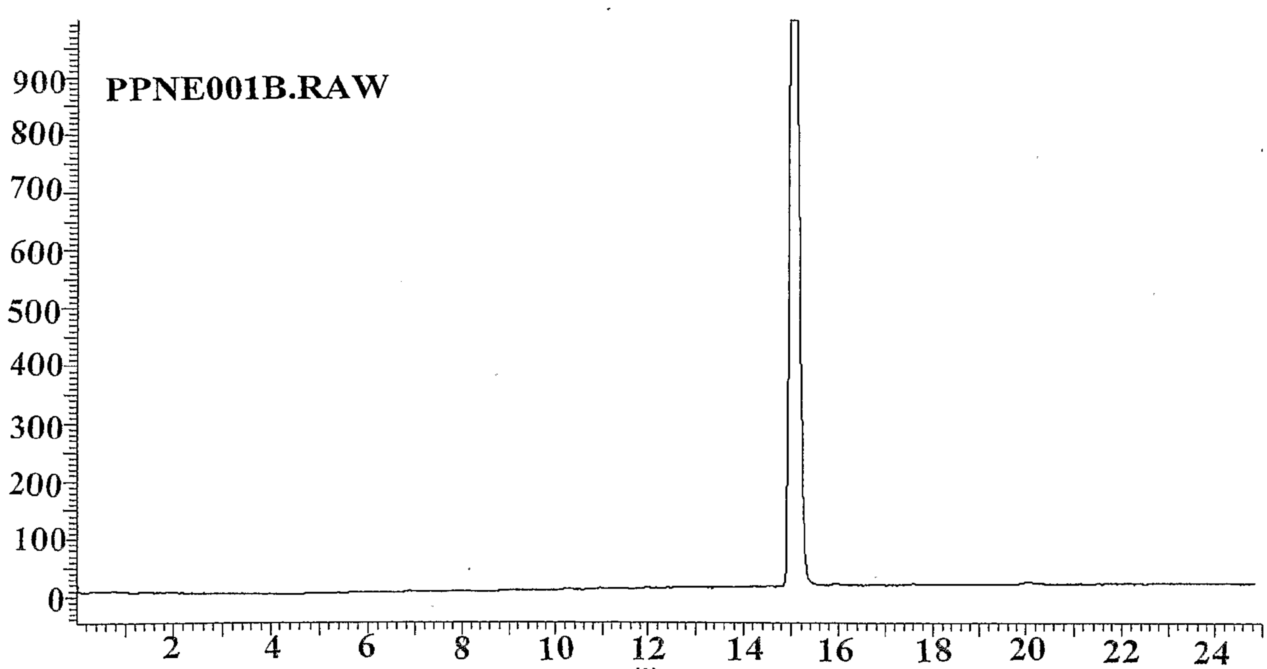


(j)

Fig. 9 (continued)

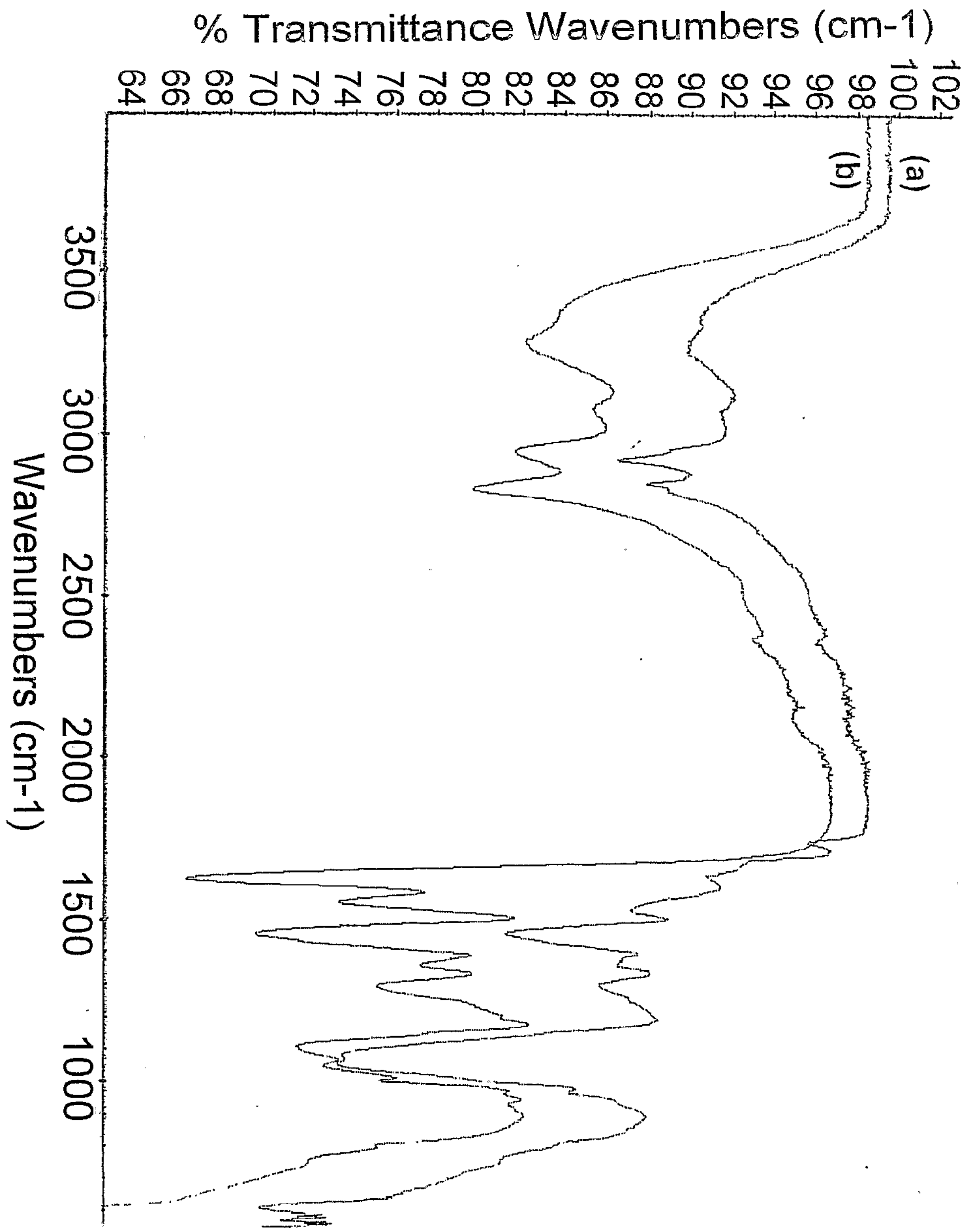


(k)



(l)

Fig. 10


% Transmittance Wavenumbers (cm-1)
64 66 68 70 72 74 76 78 80 82 84 86 88 90 92 94 96 98 100 102
(a)
(b)
3500 3000 2500 2000 1500 1000
Wavenumbers (cm-1)

INTERNATIONAL SEARCH REPORT

International Application No
/DK2004/000330

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C08G73/02 C08F290/06 A61K31/785

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C08G C08F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/56792 A (SOLOMON DAVID HENRY ; PATRAS GEORGIA (AU); UNIV MELBOURNE (AU); QIAO G) 28 September 2000 (2000-09-28) page 1, lines 4-10 page 2, lines 5-35 page 3, line 4 - page 5, line 8 page 6, line 22 - page 7, line 13 page 8, line 13 - page 13, line 7 page 14, line 22 - page 17, line 3; claims; figures; examples -----	1-7, 13-15, 17-39, 61-63, 94,95, 107-110, 125-130

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 August 2004	14/09/2004

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL – 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer
Otegui Rebollo, J

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 134 740 A (SHEETZ DAVID P) 26 May 1964 (1964-05-26) column 1, lines 9-63; claims; examples	1-6, 19-41, 57-64, 94,95, 97-106, 125-127
X	PULFER S K ET AL: "INCORPORATION OF NITRIC OXIDE-RELEASING CROSSLINKED POLYETHYLENEIMINE MICROSPHERES INTO VASCULAR GRAFTS" JOURNAL OF BIOMEDICAL MATERIALS RESEARCH, WILEY, NEW YORK, NY, US, vol. 37, no. 2, November 1997 (1997-11), pages 182-189, XP000978327 ISSN: 0021-9304 abstract page 183, right-hand column, paragraph 2 - page 188, left-hand column, paragraph 1	1,42-46, 52,57, 59, 61-65, 67,68, 70-74, 76-79, 85, 105-107, 109
X	WO 96/39156 A (GELTEX PHARMA INC ; HOLMES FARLEY STEPHEN RANDALL (US); WHITESIDES GEO) 12 December 1996 (1996-12-12) page 3, lines 2-14 page 3, line 32 - page 4, line 10 page 9, line 16 - page 10, line 25 page 21, lines 1-19 page 36, line 10 - page 37, line 30; claim 7	1-7, 13-15, 17-41, 61-64
X	WO 02/085381 A (GELTEX PHARMA INC) 31 October 2002 (2002-10-31) page 1, line 27 - page 4, line 10 page 7, line 17 - page 8, line 12 page 11, line 22 - page 12, line 6; claims 5-9; examples 8,11	1-7, 13-15, 17-41, 61-64
X	US 3 766 299 A (DORNTE R) 16 October 1973 (1973-10-16) column 1, lines 14-20 column 2, lines 8-25 column 2, line 40 - column 6, line 55; claims; examples 1,11,12	1-4

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International Application No
[redacted]T/DK2004/000330

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FERRUTI P ET AL: "LINEAR AMINO POLYMERS: SYNTHESIS, PROTONATION AND COMPLEX FORMATION" BEHAVIOR OF MACROMOLECULES, SPRINGER VERLAG, BERLIN,, DE, vol. 58, 1984, pages 55-92, XP009034930 page 59, last paragraph - page 60, paragraph 3 page 65, last paragraph - page 69, paragraph 2 page 89, last paragraph -----	1-130
X,P	WO 03/085031 A (RADEMANN JOERG) 16 October 2003 (2003-10-16) page 1, lines 6-9 page 2, lines 11-25 page 3, line 18 - page 8, line 25; claims; figures; examples -----	1,86-93

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK2004/000330

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 131
because they relate to subject matter not required to be searched by this Authority, namely:

The subject-matter of claim 131 of the application concerns a method for treatment of the human or animal body by therapy, and thereofore no search will be established for said claim (Rule 39.1(iv) PCT).

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/DK2004/000330

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0056792 A	28-09-2000	WO 0056792 A1	28-09-2000
		AU 760792 B2	22-05-2003
		AU 3264400 A	09-10-2000
		EP 1187859 A1	20-03-2002
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		AU 5974296 A	24-12-1996
		EP 0831857 A2	01-04-1998
		JP 11512074 T	19-10-1999
		NZ 309548 A	28-07-2000
		WO 9639156 A2	12-12-1996
		US 2003133902 A1	17-07-2003
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